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BLEEDING, THROMBOSIS AND VASCULAR BIOLOGY

XXVIII Congresso Nazionale SISET

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Bleeding, Thrombosis and Vascular Biology

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Il **XXVIII Congresso Nazionale della Società Italiana per lo Studio dell'Emostasi e della Trombosi (SISET)** si terrà a Roma dal 6 al 9 Novembre 2024. Si tratta di un importante evento scientifico organizzato da SISET, società che conta più di 800 membri provenienti dalle aree specialistiche mediche, biologiche e biotecnologiche e che condividono l'interesse per le patologie tromboemboliche ed emorragiche.

Le malattie tromboemboliche (arteriose e venose), costituiscono la principale causa di mortalità e morbilità nei paesi occidentali. Pertanto, la loro diagnosi, prevenzione e trattamento, sono oggetto di continui studi e i progressi in questo campo della medicina sono stati negli ultimi anni rapidi e sempre in evoluzione. In particolare, lo sviluppo di nuovi farmaci ha offerto importanti vantaggi nella prevenzione dell'ictus e nella terapia del tromboembolismo venoso e il loro impiego in altri tipi di patologie quali i tumori e sono tuttora oggetto di studio.

Le malattie emorragiche congenite (quali ad esempio l'emofilia, la malattia di von Willebrand, le piastrinopatie) e acquisite (piastrinopenia immune, cirrosi epatica, coagulopatia da consumo) costituiscono una importante sfida diagnostica e terapeutica anche per gli specialisti del settore e richiedono un costante aggiornamento. Anche in questo ambito, nuove prospettive terapeutiche si sono affacciate all'orizzonte e stanno cambiando radicalmente il modo di gestire soprattutto i pazienti affetti da emofilia, che è la patologia emorragica congenita più diffusa nella popolazione generale.

Le problematiche trombotiche ed emorragiche verranno approfondite sia dal punto di vista fisiopatologico che dal punto di vista clinico; sarà inoltre data particolare attenzione alle tematiche della salute della donna e del bambino, e alla gestione di situazioni complesse quali la contemporanea presenza di rischi trombotici ed emorragici in un medesimo scenario clinico.

Il Congresso SISET rappresenta una grande occasione per tutti i ricercatori italiani di incontrarsi e presentare gli ultimi risultati degli studi clinici e di ricerca di base che sono condotti nei centri universitari e ospedalieri del nostro Paese. Verranno presentati i prodotti della ricerca più avanzata nel settore attraverso **sessioni di comunicazioni orali e poster**, selezionando le migliori comunicazioni che saranno esposte in seduta plenaria. Il Congresso offrirà l'opportunità del più ampio aggiornamento sulle principali tematiche nel campo delle patologie tromboemboliche ed emorragiche, che sarà presentato dai più affermati esperti italiani del settore in **16 Sessioni educazionali e di esame dello "state of the art"**, con argomenti incentrati su ricerca di base, biologia vascolare, medicina clinica, e di laboratorio. Gli aspetti educazionali saranno arricchiti anche da **4 Simposi congiunti** in cui SISET si confronterà su temi di comune interesse con relatori identificati da altre Società Scientifiche attive nel settore delle patologie trombotiche ed emorragiche (AICE, FADOI, FCSA, SIAPAV, SIC, SIMI, SIMTI, SISA). Nel programma è anche previsto un **Simposio inaugurale** dedicato alle tematiche dell'Intelligenza Artificiale nella ricerca scientifica e ai sistemi di gestione clinica assistiti dall'informatica e un **Simposio Presidenziale**, che affronterà il tema della trombofilia e della profilassi antitrombotica. In entrambi i Simposi parteciperanno prestigiosi esperti internazionali e nazionali per offrire letture magistrali di altissimo livello. Sarà prevista anche una **Sessione "SISET Giovani"**, gestita dal Gruppo di Studio Giovani e dedicata all'aggiornamento sul tema delle malattie infiammatorie croniche intestinali.

Essendo l'emostasi, per sua natura, trasversale a tutte le discipline mediche il Congresso è rivolto a tutti coloro che svolgono attività di ricerca e/o assistenziale (ematologi, internisti, cardiologi, neurologi, pneumologi, rianimatori, chirurghi, ginecologi, biologi, biotecnologi), esperti nella diagnostica strumentale e di laboratorio e infermieri. Tutti accomunati da un interesse particolare e entusiasta che è stato riassunto nel **motto del Congresso "La Passione del Sapere"**.

Valerio De Stefano
Presidente SISET

The **XXVIII National Congress of the Italian Society for the Study of Hemostasis and Thrombosis (SISET)** will take place in Rome from November 6 to 9, 2024. This important scientific event is organized by SISET, which has over 800 members from various fields, including specialized medicine, biological sciences, and biotechnology. All members share a common interest in thromboembolic diseases and hemorrhage.

Thromboembolic diseases, both arterial and venous, are a leading cause of mortality in the European Union. Consequently, their diagnosis, prevention, and treatment are ongoing subjects of research, with significant advancements occurring in recent years. Notably, the development of new medications has greatly enhanced the prevention of strokes and the treatment of venous thromboembolism. These new therapies are also being explored for use in other conditions, such as cancer.

Congenital hemorrhagic diseases, including hemophilia and von Willebrand's disease, along with acquired conditions like immune thrombocytopenia and liver cirrhosis, present considerable diagnostic and therapeutic challenges for specialists in the field. Continuous updates are essential in this area. New therapeutic approaches are emerging that are significantly changing the management of patients with hemophilia, the most prevalent congenital hemorrhagic disorder. The congress will explore thrombotic and hemorrhagic issues from both pathophysiological and clinical perspectives. Special attention will also be given to the health concerns of women and children, as well as the management of complex situations where both thrombotic and hemorrhagic risks are present simultaneously.

The SISET Congress offers a valuable opportunity for Italian researchers to connect and showcase the latest results from clinical and basic research conducted in universities and hospitals across the country. The forefront of research in this field will be presented through **oral communications and poster sessions**, with the best presentations selected for a plenary session. The Congress will facilitate a comprehensive update on key topics related to thromboembolic and hemorrhagic diseases, delivered by established Italian experts. There will be **16 educational or "state of the art" sessions** in areas such as basic research, vascular biology, clinical medicine, and laboratory practices. Additionally, the educational content will be enhanced by **four joint symposia**. During these sessions, SISET will collaborate with other scientific societies engaged in thrombotic and hemorrhagic pathologies (AICE, FADOI, FCSA, SIAPAV, SIC, SIMI, SIMTI, SISA) to discuss topics of mutual interest.

The program also includes an **Inaugural Symposium** on the themes of Artificial Intelligence in scientific research and Information Technology-Assisted Clinical Management Systems, along with a **Presidential Symposium** addressing thrombophilia and antithrombotic prophylaxis. Both symposia will feature renowned national and international experts who will deliver high-level lectures. Additionally, there will be **a session titled "SISET Young,"** organized by the Young Study Group, dedicated to updates on chronic inflammatory bowel disease.

Hemostasis is a fundamental aspect of all medical disciplines, which is why the Congress is aimed at everyone involved in research and healthcare. This includes hematologists, internists, cardiologists, neurologists, pulmonologists, anesthesiologists, surgeons, gynecologists, biologists, biotechnologists, diagnostic equipment experts, and nurses. All attendees share a passionate and enthusiastic interest in this field, encapsulated in the **Congress motto: "The Passion of Knowledge."**

Valerio De Stefano
President of SISET

XXVIII Congresso Nazionale SISET

Roma

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Selected oral communications

CO001

PROGNOSTIC ROLE OF CTPA FINDINGS IN PATIENTS WITH ACUTE PULMONARY EMBOLISM: DATA FROM THE COPE STUDY

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Background and Aims: Diagnosis and prognostic assessment of patients with acute pulmonary embolism (PE) can be evaluated by a single test: computed tomography angiography (CTPA). The aim of this analysis is to describe the clinical features, management and short-term course of patients with acute PE included in the COPE Registry according to embolic localization and right ventricle dysfunction (RVD) status as assed at CTPA.

Methods: COPE (COntemporary management of acute Pulmonary Embolism) is a nationwide registry that was run in Internal Medicine, Cardiology and Emergency Departments in Italy and reported on in-hospital and 30-day mortality and major bleeding in 5,213 patients admitted for acute PE at 182 hospitals in Italy from 2018 to 2020. For the purpose of this study only patients with data on embolic localization or RVD at CTPA available were considered.

Results: Overall, data on embolic localization at CTPA was reported in 3754 patients: in 2207 was central (58.8%), 1327 segmental (35.3%) and 220 subsegmental (5.9%). RVD at CTPA was assessed in 571 patients and was present in 70.9%. Localization of emboli was central in 36.9%, 51.4%, 83.4% and 84.7% of patients categorized as low, intermediate-low, intermediate-high, and high-risk according to ESC model. RVD at CTPA was present in 23.9%, 57.7%, 88.9%, and 100% of patients at low, intermediate-low, intermediate high and high risk according to the ESC model. In the overall study population, not central localization of emboli (HR 0.81, 95% CI 0.59-1.12), but hemodynamic instability (HR 5.61, 95% CI 3.47-9.07) was associated with increased risk of 30-day all-cause death. Similarly, central localization of emboli was not associated with death due to PE (HR 1.98, 95% CI 0.97-4.05) but hemodynamic instability was (HR 9.15, 95% CI 4.57-18-32). In hemodynamically stable patients, central localization of emboli was associated with an increased risk of death due to PE (HR 2.36, 95% CI 1.07-5.22) (Figure 1). No significant increase in the risk of 30-day all-cause death nor of death due to PE (HR 1.12, 95% CI 0.40-3.15, HR 1.36, 95% CI 0.28-6.74, respectively) was observed in patients with RVD at CTPA compared to those without; the presence of hemodynamic instability was associated with increased risk of all-cause (HR 5.18, 95% CI 1.96-13.65), but not of PE-related (HR 3.34, 95% CI 0.68-16.40) death.

Conclusions: Central localization of emboli and RVD assessed at CTPA are prevalent in patients categorized as ESC intermediate-high or high risk. In patients with acute PE, the main determinant for adverse outcome is the presence of hemodynamic instability, while central localization of emboli is associated with death due to PE in hemodynamically stable patients.

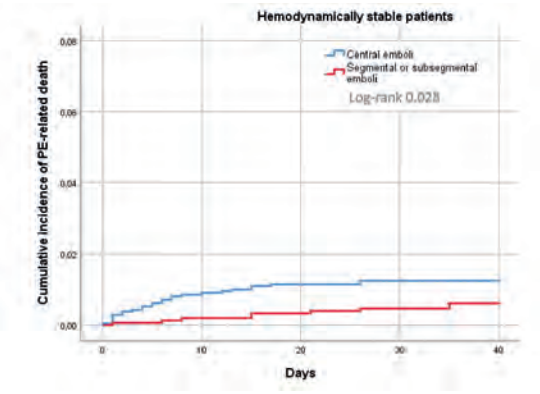

Figure 1.

CO002

VON WILLEBRAND FACTOR NATURAL VARIANTS OF THE ARGININE 1205: IN-SILICO ANALYSIS OF THE PROTEIN STRUCTURAL CHANGES AND ITS INTERACTIONS WITH THE MACROPHAGIC SCAVENGER RECEPTOR LRP1

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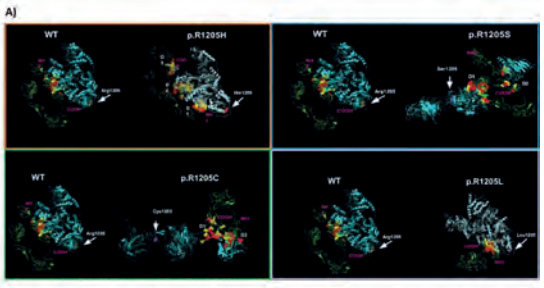
Background and Aims: The Vicenza variant of the von Willebrand Factor (VWF) p.R1205H is associated to a clinical phenotype of von Willebrand Disease type 1 and characterized by a quantitative reduction of the VWF in the circulation due to an increased clearance. Although the biomolecular mechanisms of the accelerated clearance are still not well known, it has been demonstrating an implication of the macrophagic scavenger receptor LRP1 and its interaction with the VWF, rather than the multimeric size. Indeed, other natural variants, such as p.R1205S, p.R1205C and p.R1205L, determine a reduction of the VWF half-life, confirming the direct role of the R1205 in regulating the half-life of the mature VWF protein. This study aims to globally analyze in-silico the structural consequences of the VWF p.R1205H, p.R1205S, p.R1205C and p.R1205L variants, which could be responsible for the increased VWF binding affinity to the LRP1. These modeling methods are used as strategy to investigate a macromolecule such as the VWF, in order to set the basis for a better comprehension of the VWF clearance and the involvement of the D'D3 in the VWF-FVIII complex half-life in the circulation.
Methods: I-TASSER and FG-MD software were used to predict the conformation of the monomeric VWF WT and R1205 variants and the structure of the LRP1 Cluster-IV. The docking of the complexes VWF variants-LRP1 were performed by ClusPro program. The involved domains and chemical bonds were predicted by using PDBsum platform. PRODIGY program was used to investigate the binding affinity through ΔG and Kd calculation.
Results: The substitution in the p.R1205H variant results in the lack of the Arg1205-Asp1249 hydrogen bond, altering the surrounding region 1134-1298 and producing allosteric rearrangements in the three regions involving the Gln1311-Arg1315 (D1), Thr1547-Ser1932 (D2), and Ser1953-Gln2140 (D3) segments. Indeed, compared to the WT, the p.R1205H docking showed a major presence of salt and hydrogen bonds with the LRP1 and even a different orientation of the VWF interaction sites, thus an increased predicted interaction affinity. The p.R1205S and p.R1205C variants cause the "widening" of the VWF monomers, by bridging the LRP1 between two regions of the variants; for the p.R1205S, the two interacting regions are the Arg1399-Glu1567 (D1) and Asp1897-Thr2158 (D2), whereas, in the case of p.R1205C, are the Asn1396-Thr11945 (D1) and the Gly2044-Val2191 (D2) regions. Finally, the p.R1205L variant induces VWF conformational changes involving the region Arg865-Asp952 in the LRP1 binding, but the interaction surface and the binding affinity were not significantly perturbed (Figure 1A). The Figure 1 B summarizes the ΔG and Kd values at 37°C for each interaction.
Conclusions: From these results, it seems that VWF R1205 variants could remove the inhibitory role of the D'D3 domain, accelerating the VWF clearance by alterations of the VWF-LRP1 interaction. The knowledge of the functional behavior of these natural variants has demonstrated the involvement of amino acid residues clustered within the D'D3 and A1A2A3 domains in the VWF and VWF-FVIII complex half-life in the circulation. In particular, the VWF p.R1205H, p.R1205S, and p.R1205C variants could even create a novel receptor-binding site for the LRP1 within the D'D3 domains from Gln1311 to Gln2140. Further *in-vitro* and *ex-vivo* studies are needed to better understand the contribution of the LRP1 function in the VWF clearance.



B) CALCULATED ΔG OF BINDING OF DIFFERENT WT MONOMER SPECIES AND LRP1-CLUSTER IV WITH THE CORRESPONDING K_D VALUES CALCULATED BY THE PRODIGY PROGRAM (T=37 °C)

SPECIES	ΔG (Kcal mol^{-1})	K_d (M)
WT	-18.9	$5x10^{-14}$
P.R1205H	-26.8	$1x10^{-19}$
P.R1205S	-24.8	$3.5x10^{-18}$
P.R1205C	-22.8	$8.8x10^{-17}$
P.R1205L	-18.7	$6x10^{-14}$

Figure 1.

CO003

RISK OF PREGNANCY COMPLICATIONS AND EFFECTS OF DIFFERENT ANTITHROMBOTIC PROPHYLAXIS STRATEGIES IN WOMEN WITH ESSENTIAL THROMBOCYTHEMIA: A RETROSPECTIVE MONOCENTER ANALYSIS OF 100 PREGNANCIES

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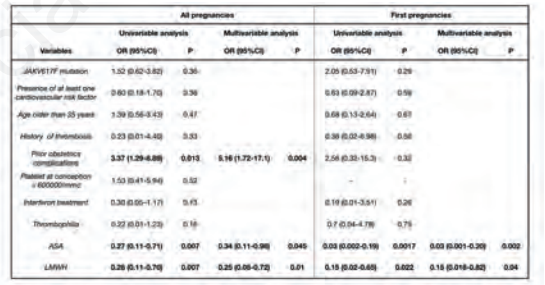
Background and Aims: Approximately 20% of pts with essential thrombocythemia (ET) are under 40, making pregnancy a common occurrence. They have a higher risk of obstetric complications, resulting in a 60% live birth rate. This study aims to evaluate and effectiveness and safety of low-dose aspirin (ASA) alone, low-molecular-weight heparin (LMWH) alone, or a combination of both in pregnant ET pts.
Methods: This retrospective study analyzed all pregnancies following an ET diagnosis from 1978 to 2023 in our ET dataset. The outcomes evaluated were thrombosis, obstetric complications, and bleeding.
Results: We analyzed 100 ET-related pregnancies in 61 women. The median age at diagnosis and first pregnancy after diagnosis was 33 yrs (range 1-44) and 34 yrs (range 22-44), respectively. Thirty (49.1%), 7 (11.5%) and 4 (6.6%) women carried the JAK2V617F, calreticulin, and MPL gene mutations, respectively; 20 (32.8%) women were triple negative. Three pts (4.9%) had a history of TIA (n=2) and Budd-Chiari syndrome (n=1), 8 had thrombophilia (13.1%), and 16 (26.3%) had at least one cardiovascular risk factor. Twenty-two pregnancies (29.7%) were treated with ASA, 12 (16.2%) with LMWH, and 49 (66.2%) with both; out of 20 pregnancies in 11 pts with previous thrombosis or thrombophilia, 10 were treated with LMWH +/- ASA. The live birth rate was 74%; the median gestational age at delivery was 39 wks (range 30-42), and the median birth weight was 3170 gr (range 870-4400). The median gestational age of the 24 miscarriages was 8 wks (range 5-18). Additionally, two intrauterine deaths occurred at 23 and 29 wks of pregnancy. Obstetric complications occurred in 25% of pregnancies, most frequently intrauterine growth retardation (7%) and placental disorders (5%). No thrombotic or bleeding antepartum events were recorded. Ttwo women had post-partum VT: one involving cerebral veins concurrently with otomastoiditis and without antithrombotic prophylaxis, and one involving a deep leg vein during LMWH. Six women had postpartum hemorrhage, 5 of them receiving peripartum LMWH. Multivariable analysis (Table 1) showed that previous obstetric complications increased the risk of pregnancy loss (odds ratio, OR 5.16, 95%CI 1.72-17.1, p=0.004), whereas ASA or LMWH had protective effects (ASA: OR 0.34, 95%CI 0.11-0.98, p=0.045; LMWH: OR 0.25, 95%CI 0.06-0.72, p=0.01). When analysis was restricted to first ET-related pregnancies, ASA and LMWH maintained their protective effects (ASA OR 0.03, 95%CI 0.001-0.2, p=0.002; LMWH OR 0.15, 95%CI 0.018-0.82, p=0.01). The effectiveness of ASA+LMWH was not significantly higher than ASA alone or LMWH alone (in all pregnancies OR 0.66, 95%CI 0.19-2.32, p=0.52 and OR 0.97, 95%CI 0.18-5.32, p=0.97, respectively; in the first pregnancies OR 0.22, 95%CI 0.008-5.75, p=0.36 and OR 0.06, 95%CI 0.003-1.48, p=0.09, respectively). The JAK2 V617F mutation was not a risk factor for obstetric complications.
Conclusions: In our study, both ASA and LMWH were found to effectively prevent obstetric or thrombotic complications without increasing the risk of antepartum bleeding. A combined regimen did not prove to be superior to either ASA or LMWH alone, but the small sample size warrants caution. In conclusion, ASA may be the preferred treatment for ET pregnancies, while the addition of LMWH should be considered for patients with a history of VT or additional risk factors for VT. Furthermore, the presence of the JAK2V617F mutation was not found to be associated with a higher rate of pregnancy losses.

Table 1.



	All pregnancies				First pregnancies			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variables	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
JAKV617F mutation	1.52 (0.62-3.82)	0.36			2.05 (0.53-7.91)	0.29		
Presence of at least one cardiovascular risk factor	0.60 (0.18-1.70)	0.36			0.53 (0.09-2.87)	0.59		
Age older than 35 years	1.39 (0.56-3.43)	0.47			0.68 (0.13-2.64)	0.67		
History of thrombosis	0.23 (0.01-4.40)	0.33			0.38 (0.02-6.98)	0.56		
Prior obstetrics complications	**3.37 (1.29-8.89)**	**0.013**	**5.16 (1.72-17.1)**	**0.004**	2.56 (0.32-15.3)	0.32		
Platelet at conception < 600000/mmc	1.53 (0.41-5.94)	0.52			-	-		
Interferon treatment	0.30 (0.05-1.17)	0.13			0.19 (0.01-3.51)	0.26		
Thrombophilia	0.22 (0.01-1.23)	0.19			0.7 (0.04-4.78)	0.75		
ASA	**0.27 (0.11-0.71)**	**0.007**	**0.34 (0.11-0.98)**	**0.045**	**0.03 (0.002-0.19)**	**0.0017**	**0.03 (0.001-0.20)**	**0.002**
LMWH	**0.26 (0.11-0.70)**	**0.007**	**0.25 (0.06-0.72)**	**0.01**	**0.15 (0.02-0.65)**	**0.022**	**0.15 (0.018-0.82)**	**0.04**

Odds ratio for pregnancy loss in ET-related pregnancies. The low number of first pregnancies with a platelet count at conception precluded any estimation.

CO004

TAILORED COLLAGEN BINDING CONFERS DISTINCT FUNCTIONAL PROPERTIES TO ENGINEERED FACTOR IX FUSION PROTEINS IN HEMOPHILIA B MOUSE MODEL

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Background and Aims: The efficacy of hemophilia B (HB) replacement therapy is evaluated based on the

activity levels of coagulation factor IX (FIX) in plasma. However, the evidence that FIX bound to extravascular type IV collagen (Col4) contributes to efficient hemostasis, even at FIX plasma levels <1%, and affects the biodistribution of infused recombinant FIX, has emerged as a relevant component for treatment optimization. In this scenario, the impact of Col4 binding on the pharmacokinetic (PK) profile of FIX has been poorly addressed, especially in the context of long-acting albumin/IgG fusion proteins, whose prolonged half-life is due to a neonatal Fc receptor (FcRn)-mediated recycling mechanism. Here, we investigated the impact of amino acid substitutions improving ($^{+}$) or decreasing/abolishing ($^{-}$) Col4 binding, on the pharmacokinetic (PK) profile of gain-of-function (^{G}) FIX joined with a human serum albumin (HSA) variant endowed with improved FcRn engagement (HSA_{eng}).

Methods: Engineered variants, expressed in HEK293 cells, were purified and characterized for functional (aPTT) and binding (ELISA-based; Surface Plasmon Resonance, SPR; cellular recycling assay) properties, and administered to mice for PK studies (protein and activity levels).

Results: The panel of designed variants was created by engineering steps of the fusion protein with both fusion partners wild-type (FIX-HSA), which resulted in FIX^{G}-HSA_{eng} that served as scaffold for further modifications producing FIX^{G+}-HSA_{eng} and FIX^{G-}-HSA_{eng}. In comparison with FIX-HSA, the FIX^{G+}-HSA_{eng} and FIX^{G-}-HSA_{eng} variants displayed i) hyperactive properties (6-12 fold), ii) improved binding to human (h)FcRn (K_D, 0.2-0.3 nM; FIX-HSA, mean K_D 180 nM), iii) a parallel improvement in cellular recycling assays (10-15 fold), and iv) 3-fold prolonged half-life in hFcRn-transgenic mice, characterized by normal levels of circulating FIX, indicating engineered albumin as the main modulator. In a mouse model expressing normal levels of endogenous FIX, the decreased Col4 binding negatively modulated plasma half-life of FIX^{G-}-HSA_{eng}. Differently, in mice knockout for the *F9* gene, and thus resembling CRM-negative HB, the impact of tailored Col4 binding of the FIX^{G+}-HSA_{eng} and FIX^{G-}-HSA_{eng} variants exerted opposite effects on the PK and biodistribution profiles, with half-life values of 26 and 17 hours, respectively, in comparison with the reference FIX-HSA fusion protein (22 hours). Noticeably, FIX^{G-}-HSA_{eng} showed negligible extravascular distribution, and the highest plasma levels at early time points, followed by the steepest decay curve. In contrast, the early extravascular biodistribution of FIX^{G+}-HSA_{eng} resulted in increased levels in liver, kidneys, lungs, and knee joints (2-3 fold than FIX-HSA). Importantly, FIX^{G+}-HSA_{eng} displayed an extraordinarily prolonged functional half-life (80 hours) in comparison with the other fusion proteins (range 22-30 hours).

Conclusions: Our data contribute new knowledge on the impact of Col4 binding in the context of FIX fusion proteins, supporting the use of FIX^{G-}-HSA_{eng} and FIX^{G+}-HSA_{eng} as hyperactive short- or long-term treatment options, with relevant implications for personalization of HB replacement therapy.

CO005

FACTOR IX ACTIVITY LEVELS SUSTAINED AFTER GENE THERAPY IN HAEMOPHILIA B GENE THERAPY: HOPE-B ETRANACOGENE DEZAPARVOVEC PHASE 3 TRIAL RESULTS

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Background and Aims: The Phase 3 HOPE-B trial (NCT03569891) assesses etranacogene dezaparvovec, a gene therapy for haemophilia B comprising an adeno-associated virus 5 (AAV5) vector and codon-optimised factor IX (FIX) Padua R338L transgene under the control of a liver-specific promoter. Aim of this report is to communicate FIX activity levels at 3 years post-treatment.

Methods: Adult (≥18 years) male participants (n=54) with severe or moderately severe haemophilia B (FIX ≤2%) were treated in the Phase 3, open-label, single-arm, pivotal HOPE-B trial with a one-time intravenous infusion of 2×10^{13} gc/kg etranacogene dezaparvovec, following a ≥6-month lead-in period of their usual FIX prophylaxis.

Results: Of 54 participants receiving etranacogene dezaparvovec, 52 completed 3-year efficacy follow-up and 53 completed 3-year safety follow-up. Mean annualized bleeding rate (ABR) for all bleeds during Months 7-36 was reduced by 64% *versus* lead-in (1.52 and 4.17, respectively; p=0.0004). Two (3.7%) participants - one with the highest AAV5 NAb titre 1:3212 and one who received partial dose (~10%) - did not express FIX Padua and remained on FIX prophylaxis. By year 3, 1 (1.9%) patient expressed endogenous FIX activity levels <5 IU/dL, 3 (5.6%) between 5<12 IU/dL), 12-<40 IU/dL for 26 (48.1%), and 40-100 IU/dL for 18 (33.3%). At 3 years post-treatment, the mean±SD (median; range) FIX activity level of participants was 38.6 IU/dL±17.8 (36.0; 4.8–80.3) for the 48 patients for whom endogenous FIX levels were available and interpretable. FIX levels were missing/uninterpretable for 4 (7.4%) patients: one died [unrelated to treatment], one returned to FIX continuous prophylaxis at month 30 post-treatment following decline of FIX expression to levels 2-5 IU/dL and bleeding phenotype recurrence, one had a liver transplant, one participant's sample was unsuitable for analysis due to hemolysis. 11 of 54 (20.4%) participants had early ALT elevations, of whom 9 received reactive steroids. All participants who had early ALT elevations, expressed FIX activity levels <40 IU/dL. No late treatment-related ALT elevations or thromboembolic events were reported. Overall safety

profile remained favourable and consistent with previous observations.
Conclusions: One-time infusion of etranacogene dezaparvovec resulted in stable FIX expression, with 53.7% patients maintaining mild- and 33.3% maintaining non-haemophilia (>40 IU/dL) FIX activity levels at 3 years post-treatment.
COI: Giancarlo Castaman: Bayer, BioMarin, Bioviiix, CSL Behring, LFB, Novo Nordisk, Pfizer, Roche, SOBI,, Takeda, uniQure; Cedric Hermans : Bayer, BioMarin, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Rocher, SOBI, Takeda, uniQure; Michiel Coppens: Alexion, Anthos, Bayer, CSL Behring, Daiichi Sankyo, Novo Nordisk, OctaPharma, Pfizer, Roche, Sobi, Spark, Viatris; Sandra Le Quellec: CSL Behring; Nicholas Galante: CSL Behring; Karen Pinachyan: CSL Behring; Steven Pipe: Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, HEMA Biologics, Freeline, LFB, Novo Nordisk, Pfizer, Regeneron/Intellia, Genentech/Roche, GeneVentiv and Equilibra Bioscience, Sanofi, Takeda, Spark Therapeutics, uniQure, Siemens.

CO006

REVERTING HIGHLY FREQUENT F8 NONSENSE MUTATIONS: BASE AND PRIME EDITING APPROACH FOR HEMOPHILIA A

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Background and Aims: Among F8 gene alterations causing Hemophilia A (HA), nonsense mutations are relatively frequent (>10%), with virtually undetectable plasma factor VIII (FVIII) levels. Base (BE) and Prime (PE) editing are emerging as molecular tools able to accurately edit the genomic DNA, thus rescuing gene expression. These approaches would require a single intervention, thus potentially ensuring a life-long cure for HA patients. This work challenges BE and PE tools over the highly-frequent F8 nonsense mutations to restore biosynthesis/secretion of functional FVIII.
Methods: Design of BE and PE tools to revert the TGA>CGA triplet. Transient expression studies in HEK293 of FVIII fused with Gaussia luciferase (FVIII-GL) or B-domain deleted FVIII expression cassette bearing nonsense mutations. Luciferase evaluation followed by ELISA/aPTT assays on media after BE and PE transfection. Further evaluation of correction was performed in HEK293 stable clones.
Results: We selected highly frequent F8 nonsense variants (n=9) arising from CGA(Arginine)>TGA change and representative of 403/1053 (40%) HA patients. The optimized FVIII-GL bearing nonsense variants were exploited to screen, through evaluation of luciferase expression levels, BE and PE editing efficiency. Noticeably, the p.R355X, p.R602X, p.R814X, p.R2166X and p.R2228X variants were efficiently rescued (from barely detectable to 5-42.5% of FVIII-GL WT) with both approaches, thus prompting us to further investigate FVIII native-sequence rescue. In particular, BE and PE were challenged in cellular models transiently or stably expressing a B-less FVIII construct bearing nonsense mutations. In both models, BE and PE transfection efficiently rescued FVIII secretion (10-60%) and activity (4.3-51%). Importantly, the correction was further validated at DNA level, which revealed the reversion of the TGA into CGA triplet.
Conclusions: Our data provide a novel correction approach for nonsense mutations, proposing BEs and PEs as powerful tools to permanently revert, with a single intervention, highly frequent F8 nonsense mutations, rescuing the expression of a functional FVIII. This experimental evidence, provided for the first time in the coagulation field for nonsense mutations, opens the way for the development of an innovative therapeutic approach in tailored HA animal model.

CO007

BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) IN CARDIOVASCULAR AGING

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Background and Aims: Aging is a physiological process that is part of natural course of life cycle. As people age, they encounter a complex interplay of biological changes that affect their overall health and well-being. Thrombosis poses a significant risk in older adults and can lead to severe complications such as myocardial infarct and strokes. Understanding the mechanisms underlying thrombosis associated with aging is critical for developing more effective preventive and therapeutic strategies to mitigate its impact of thrombosis on older populations. Emerging research has shed light on the potential role of Brain-Derived Neurotrophic Factor (BDNF) in cardiovascular system and has shown that BDNF influences platelet activity, coagulation pathways, endothelial proliferation, vascular remodelling and inflammation. Low BDNF levels have been found in brain and in plasma from older adults, and have been associated to myocardial infarction. The aim of this study was to examine whether a reduction in BDNF levels occurs and influences vascular aging predisposing to thrombosis.
Methods: Young (3-4 months), middle-age (12 months) and old (18-22 months) wild type (WT) and knock-in mice with low BDNF levels ($BDNF^{Met/Met}$) were used. Carotid artery thrombosis was induced by $FeCl_3$ application and blood flow was recorded by a transonic flowmeter. Platelet functionality was evaluated by flow cytometry. Genes differentially expressed in aorta tissue were

identified by RT-PCR senescence array and following confirmed by qPCR and western blotting. BDNF levels were measured by ELISA Kit, RT-PCR and/or western blotting.
Results: BDNF levels in WT aorta tissue decreased progressively with age, reaching, at 12 months, levels comparable to that measured in young $BDNF^{Met/Met}$ mouse. Consistent with previous results, we showed that leucocyte and platelet count and percentage of platelet/leucocyte aggregates increased with age in WT mice, as well as arterial thrombosis was enhanced in old WT mice compared to young WT mice. Interestingly, young $BDNF^{Met/Met}$ mice had a higher number of blood circulating cells, a greater propensity to form platelet/leucocyte aggregates, and a shorter mean time to developed a total carotid occlusion in response to $FeCl_3$ than young WT mice, showing a similar prothrombotic profile than old WT mice. Senescence arrays indicated that aorta tissue from middle-age $BDNF^{Met/Met}$ mice and old WT mice have similar gene expression profiles, and that samples from young $BDNF^{Met/Met}$ mice interchanged with that of middle-age WT mice. Validation of genes emerged from senescence array (p16, p19, p2, p53, Nfil3 CLOCK-gene expression and MM9) supported the hypothesis of a premature aging profile of $BDNF^{Met/Met}$ mice. Remarkable, a negative correlation was found between BDNF and the analysed aging genes, suggesting a link between reduced BDNF levels and aging. Finally, we observed a high rate of mortality in $BDNF^{Met/Met}$ mice compared to WT mice (35% *versus* 1%). Only 13 of 20 mutant mice survived over 18 months.
Conclusions: Taken together these data indicate that: a) BDNF decreases in aorta during aging; b) the reduced BDNF levels go hand by hand with increased expression of genes associated with cell senescence; c) a mouse model with low BDNF levels displays a premature aging. Our study suggests a possible role of BDNF in vascular aging. Weather the administration of exogenous BDNF or its modulation can help to prevent senescence remains to be further explored.

CO008

CHARACTERIZATION OF ENDOTHELIAL FUNCTION AND ANGIOGENESIS IN GLANZMANN THROMBASTHENIA: POSSIBLE ROLE IN GASTROINTESTINAL ANGIODYSPLASIA

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Background and Aims: Glanzmann Thrombasthenia (GT) is a rare, autosomal recessive bleeding disorder caused by variants in ITGA2B or ITGB3 genes, coding respectively for the αIIb and β3 subunits of integrin αIIbβ3, the platelet receptor for fibrinogen. This results in an absent/defective receptor on the platelet surface, impaired platelet aggregation, and bleeding. Gastrointestinal angiodysplasia (GIA), a digestive tract vascular malformation due to abnormal angiogenesis, may lead to severe gastrointestinal bleeding (GIB), strongly contributing to the severe bleeding phenotype of GT patients[1]. Several cases of GIA in GT patients have been reported in the literature[2-4]. While αIIbβ3 is not expressed by endothelial cells (ECs), αvβ3, which shares the β3 subunit with αIIbβ3, is expressed in ECs and plays an important role in angiogenesis. Based on these premises, we hypothesized that patients with GT due to ITGB3 variants may present with abnormal EC function. The aim of this study was to shed light on the impact of ITGA2B and ITGB3 variants on EC function, in particular proliferation, migration, and angiogenesis.
Methods: ITGB3 was silenced in Human Umbilical Vein ECs (HUVECs) by siRNA (ITGB3-depleted HUVEC). Proliferation was assessed by EdU cell proliferation assay, migration by scratch-wound healing assay, and angiogenesis by Matrigel-based tube formation assay. Endothelial Colony Forming Cells (ECFCs) were differentiated from peripheral blood of 5 healthy controls (CTRL), 4 GT patients with ITGA2B mutations, and 2 GT patients with ITGB3 mutations. ECFCs differentiated from 2 CTRL, 2 GT patients with ITGA2B mutations, and 2 GT patients with ITGB3 mutations were used to assess angiogenesis by Matrigel-based tube formation assay.
Results: Compared to control siRNA-transfected HUVECs, ITGB3-depleted HUVECs showed altered function. Proliferation was slightly increased at basal level, however lack of ITGB3 resulted in inability to respond to 50 ng/ml VEGF-A. Cell migration measured as maximum distance traveled, speed and direction, and angiogenesis, measured as branching point number, total tube number and total branch length were also decreased in ITGB3-depleted HUVECs. ECFCs differentiated from GT patients with ITGB3 mutations showed significantly decreased angiogenesis compared to ECFCs from ITGA2B patients and from CTRL, as shown by decreased branching point number (CTRL=41.33±10.19; GT ITGA2B= 53.33±12.61; GT ITGB3=11.33±7.71; mean±SD; *p<0.05; **p<0.01), total tube number (CTRL=74.33±21.83; GT ITGA2B=87.33±20.79; GT ITGB3=16.17±13.59; mean±SD; *p<0.05; **p<0.01) and total branch length (CTRL=11.68±2.56mm; GT ITGA2B=13.74±2.01; GT ITGB3=3.60±2.96; mean±SD; *p<0.05; **p<0.01) (Figure 1).
Conclusions: Our results suggest that defects in neoangiogenesis may be part of the clinical characteristics of GT, possibly associated with variants affecting the β3 integrin subunit. Some discrepancies between the find-

ings in ECFCs differentiated by GT patients with ITGB3 mutations and ITGB3-depleted HUVEC require further investigation. The concept that the bleeding phenotype of GT patients may be due not only to the well-characterised platelet defect but also to a defect of ECs is novel. This may change the therapeutic approach to this disorder and lead to the development of new prognostic stratification tools.

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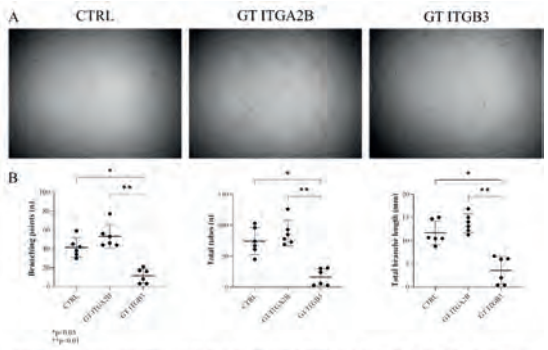

Figure: Defective angiogenesis of ECFCs differentiated from 2 GT patients with ITGB3 mutations. A) Impaired Matrigel-based tube formation assay in ITGB3 GT patient derived ECFCs compared to ITGA2B GT patient derived ECFCs and healthy control derived ECFCs. 96-well plate wells were coated with Matrigel (Corning) polymerized for at least 30 min before use. ECFCs were seeded (1.5×10^4 cells/well) in triplicate onto Matrigel. After 24 hours at 37°C, cells were imaged with a Carl Zeiss Axio Observer.A1 microscope (Carl Zeiss Inc, Oberkochen, Germany) using a 2.5x Plan-Apochromat objective and acquired using the AxioVision software (Carl Zeiss Inc). B) Angiogenesis was estimated by counting tubule number and branching points and by measuring total tube length with ImageJ (AngioTool64). All data are reported as Mean±SD. Statistical analysis was performed with One-way Anova, followed by Dunn's multiple comparisons test.

Figure 1.

CO009

RIGHT VENTRICULAR DYSFUNCTION PARAMETERS AT ECHOCARDIOGRAPHY IN PATIENTS WITH ACUTE PULMONARY EMBOLISM: META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA

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Background and Aim: Echocardiography has a crucial role for decision making on management of patient with acute pulmonary embolism (PE) according to current international guidelines. However, the definition of right ventricle dysfunction (RVD) at echocardiography requires standardization. We performed an Individual patient data meta-analysis (IPDMA) to assess the role of individual parameters of RVD and of combinations of parameters for the prediction of short-term all-cause mortality and PE-related death.
Methods: A systematic search was run to identify clinical studies reporting on RVD at echocardiography and on short-term clinical outcome in patients with acute PE. Individual patient data from the original studies were pooled to perform a meta-analysis (IPDMA). The study outcomes were short-term death defined as death occurring within 30 days from PE diagnosis and PE-related death. Multiple imputation was used for the management of missing data. The odds ratio for all cause and PE related mortality were calculated using generalized linear mixed effects model.
Results: Individual data from 9,233 patients with acute PE from 16 studies were pooled in a unique database. All cause short-term mortality occurred in 9% of patients (95% CI 0.06-0.13, I2 93%). The IPDMA was feasible for the following parameters: tricuspid anulus systolic excursion (TAPSE), estimated pulmonary artery pressure (PAP) >30mmHg, right to left ventricle diameter ratio (RV/LV)>1, hypokinesia, paradoxical septal motion, RV diameter>30 mm and McConnel sign. All these parameters, except for PAP>30mmHg and RV diameter>30 mm, were predictors of short-term all cause death in the overall population and in hemodynamically patients (Table 1). All the assessed RV findings, except for the McConnell's sign, were predictors of PE-related death (Table 1). The presence of one RVD parameter only was not associated with increased risk of all cause death (OR 1.22, 95% CI 0.97-1-54), while the presence of two parameters or ≥three parameters were (OR 1.63, 95% CI 1.24-2.15; OR 2.07 95% CI 1.59-2.69, respectively).
Conclusions: In patients with acute PE, the majority of RVD parameter at echocardiography are predictors of short-term death and of PE-related death. The higher the

number of RVD parameters the worst the prognosis. These results claim for standardization in RVD definition to guide decision making for patient management.

Table 1.

RVD parameters (n studies; n patients)	All cause death	PE related death
	OR (95% CI)	
TAPSE <16 mm (11; 6206)	1.70 (1.40-2.07)	2.59 (1.86-3.63)
Estimated PAP >30 mmHg (5; 5342)	1.18 (0.94-1.48)	1.71 (1.23-2.3)
RV/LV>1 (13; 7976)	1.56 (1.30-1.87)	2.84 (2.05-3.92)
Hypokinesia (8; 4444)	1.85 (1.48-2.31)	2.42 (1.78-3.30)
Paradoxycal septum (7; 5614)	1.49 (1.15-1.93)	1.76 (1.15-2.70)
RV diameter>30 mm (10; 6521)	1.21 (0.99-1.49)	1.47 (1.04-2.08)
McConnell's sign (2; 614)	1.90(1.05-3.45)	2.01(0.89-4.52)

CO010

DOACS FOR OLDER ADULTS WITH ATRIAL FIBRILLATION AND FALLS: RESULTS FROM THE PROSPECTIVE SINGLE-CENTRE DOAFF STUDY

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Background and Aims: Falls are one of the most fearsome events in anticoagulated older adults. The evidence concerning safety of direct oral anticoagulants (DOACs) in falling elderly patients with atrial fibrillation (AF) is still limited. The aim of the present study is the evaluation of the safety profile of anticoagulant therapy with DOACs in a cohort of elderly patients with AF, stratified according to the occurrence of falls during the observation period.

Methods: We prospectively enrolled consecutive anticoagulant-naïve patients aged 65 years and older, starting anticoagulation with DOACs for AF. The study cohort was stratified in fallers *vs.* non-fallers, according to the occurrence of at least one fall during the 2-year follow-up and bleeding outcomes were evaluated. A separate analysis was also conducted for those patients who fell multiple times (≥2 falls) during the observation period. Safety was defined according to the incidence of bleeding complications, as stated by the International Society on Thrombosis and Haemostasis (ISTH), namely major bleeding and clinically relevant non-major bleeding; among the major ones, a sub-analysis for intracranial haemorrhage was also performed. Finally, falls were defined as any episode of unintentional drop to the ground, as reported by patients themselves or as witnessed by the caregiver in case of cognitive impairment.

Results: We enrolled 524 consecutive patients. Mean age was 80.8 years and they were mostly women (54.0%). Among the study cohort, 148 patients (28.2%) presented at least one fall episode during the study period. The overall number of bleedings was 357 with 49 major bleedings (49 patients) and 308 clinically relevant non-major bleedings (196 patients). No difference was found between fallers and non-fallers for the risk of major and clinically relevant non-major bleedings, as shown in Figure 1. This result was confirmed for all the study endpoints also after the adjustment for potential confounders: major bleeding [HR: 1.04 (95%CI: 0.58–1.85)], intracranial haemorrhage [HR: 1.63 (95%CI: 0.69–3.80)], clinically relevant non-major bleeding [HR: 1.21 (95%CI: 0.83–1.76)], and all-cause death [HR: 1.51 (95%CI: 0.85–2.69)]. Moreover, no significant difference for the aforementioned endpoints was found even considering separately those patients who fell multiple times during the observation period. Finally, the presence of a prior cerebrovascular event [HR: 2.27 (95% CI: 1.12-4.62); p-value: 0.02] and polypharmacy [HR: 1.60 (95% CI: 1.08-2.39); p-value: 0.02] were the main drivers for major and clinically relevant non-major bleedings, respectively.

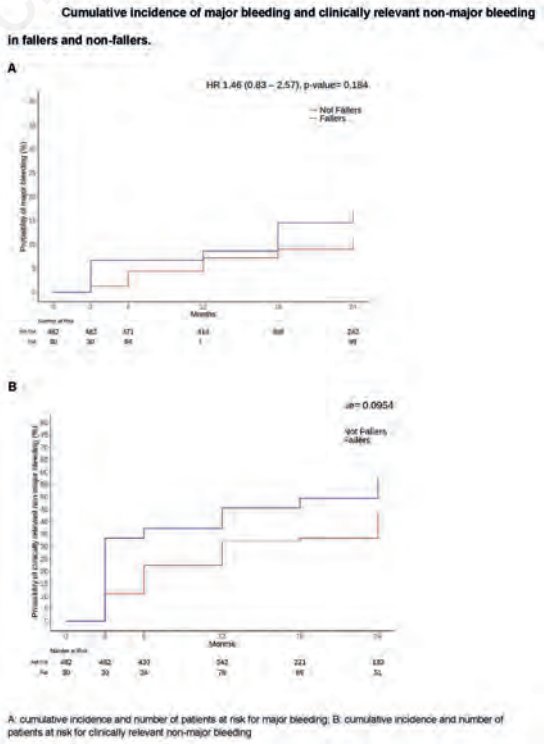

Figure 1.

Conclusions: According to our study, there would seem to be no significant difference in terms of bleed-

ings between falling and not falling elderly patients with AF, in course of anticoagulation with DOACs. This result aligns with the literature on the topic and strengths the evidence that neither the anamnestic presence of falls nor the occurrence of new falls in course of anticoagulation should dissuade clinicians from starting or continuing anticoagulant therapy. In light of this, DOACs dose reduction should be adopted only when the appropriate criteria are met. Finally, key predictors of haemorrhages showed to be a prior cerebrovascular event for major bleedings and polypharmacy for clinically relevant non-major bleedings.

CO011
FACTOR VIII REGULATES EXTRACELLULAR MATRIX PROTEINS TO STIMULATE ANGIOGENESIS AND VESSEL STABILITY

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Background and Aims: Hemophilia A (HA) is an X-linked bleeding condition resulting from mutations in the coagulation factor VIII (FVIII). The main clinical manifestation is bleeding episodes provoking/causing hemarthroses and intracranial hemorrhages. The factors that initiate hemorrhage are not known, and the onset of hemorrhage is often a random event, occurring either spontaneously or after minimal injury. Standard replacement therapies are ineffective in preventing the bleeding episodes. It is well established that FVIII is mainly secreted by endothelial cells (ECs) but there is limited understanding of the vascular stability status of HA patients, and little is known about the relationship between FVIII and endothelial function. Therefore, our aim is to investigate the role of FVIII in maintaining EC function and homeostasis.
Methods: Blood Outgrowth ECs (BOECs) from HA patients and healthy donors were isolated. HA BOECs were transduced with a lentiviral vector (LV) carrying the B-domain deleted FVIII (LV-FVIII). The transcriptomic profile of healthy, HA and LV-FVIII HA BOECs was assessed by RNA-seq technology. Healthy ECs, HA ECs, LV-FVIII HA-ECs, were used to investigate the role of FVIII in ECs function by tubulogenesis, migration, proliferation and permeability assays both *in vitro* and *in vivo* in an immunocompromised mouse model of severe HA (NSG-HA mice).
Results: HA BOECs showed *in vitro* impaired tubule network formation and endothelial cell migration capability higher permeability compared to healthy BOECs. This impaired phenotype was reverted by the re-introduction of FVIII with LV-FVIII or by treatment with recombinant human FVIII. Interestingly, both healthy and HA-BOECs respond to rhFVIII enhancing their rate of growth in a proliferation assay suggesting that FVIII could act both in physiological and pathological systems as a grow factor. The endothelial function of FVIII was also confirmed *in vivo* in NSG-HA mice, which showed that an altered angiogenesis and vessel permeability could be corrected by exogenous FVIII. The transcriptomic profiles of BOECs revealed that FVIII regulates the expression of endothelial basement membrane and extracellular matrix genes and were identified pathways corresponding to vascular development, cell migration, regulation of cell adhesion, extracellular matrix organization, and integrin cell surface interactions. These pathways were downregulated in HA *vs* C-BOECs and were rescued upon LV-FVIII transduction. Among the downregulated genes Nidogen2 was identified as one of the main FVIII regulated gene and its exogenous expression restored the extracellular matrix integrity and EC function of HA ECs.
Conclusions: The reduced EC function can be explained by the downregulated genes identified in FVIII deficient HA BOECs. Altogether, these results suggest that FVIII is not only a coagulation factor but also an endothelial cell factor which promotes vessel stability by upregulating genes involved in extracellular matrix organization. These preliminary results, if confirmed in primary ECs, can provide new insights into the possible extra-coagulative role of FVIII and it can be crucial to understand the key molecular targets missing in HA patients at the cellular level impairing EC functionality. This information can lead to novel therapeutic approaches for a safer and more efficient treatment of HA.

CO012
D-DIMER LEVELS IN PATIENTS WITH ACUTE VENOUS THROMBOEMBOLISM AND OCCULT CANCER: THE DD-NEO STUDY

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Introduction: Cancer is associated with a prothrombotic state and venous thromboembolism (VTE) can be the first manifestation of occult cancer. However, no impact on survival of extensive cancer screening in VTE has been demonstrated. Limited data are available on the association between D-dimer (DD), a non specific marker of activation of coagulation, at VTE diagnosis and occult cancer.

Objectives: To investigate whether DD levels at VTE diagnosis are associated with subsequent cancer development.

Design: Retrospective cohort conducted in a single tertiary care hospital from 2008 to 2018. Participants: consecutive patients diagnosed with symptomatic VTE and without known overt cancer underwent routine clinical evaluation and laboratory tests. In case of abnormal findings, further targeted tests were performed. Primary outcome measures: cancer development within 12 months since VTE diagnosis.

Results: 843 patients (413 women - 49%, median age 67.3 years; 10 lost to follow-up -1.2%) were included of whom 567 (67%) had unprovoked VTE. Median DD was 2,750 ng/mL (range 30-45,320) and DD was above 8,000 ng/mL in 151 patients (18%). During follow-up, 37 patients (all above 60 years) developed new cancers (4.6 percent patient years; 95% Confidence Intervals-CI:3.3-6.3). Multivariate regression showed that age above 60 years (Hazard Ratio-HR 11.7; 95% CI: 1.58-86.6; p=0.016) and DD above 8,000 ng/mL (HR: 2.5 95% CI:1.22-5.24; p=0.012) were independently associated with subsequent cancer development.

Conclusions: Patients older than 60 years at VTE diagnosis may deserve extensive screening for occult cancer, and DD above 8,000 ng/mL may be a sign an index of occult cancer.

Oral communications

CO013

THROMBOPOIETIN-RECEPTOR AGONISTS EFFICACY AND SAFETY IN PREGNANT ITP PATIENTS AND THEIR NEWBORNS: A MULTICENTER RETROSPECTIVE ITP-NET ITALIAN STUDY ON BEHALF OF GIMEMA WORKING GROUP "ANEMIA & THROMBOCYTOPENIA»

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Background: Immune thrombocytopenia (ITP) can arise de novo during pregnancy or be exacerbated by it. Specific evidence-based guidelines are lacking in this setting and the existing suggestions about management are mainly derived from non-pregnant population. Steroids (S) and immunoglobulins (IVIG) represent the main therapy for ITP during pregnancy although in some cases resistance, intolerance or adverse events related to these treatments may occur. Data on the efficacy and safety of thrombopoietin receptor agonists (TPO-RA) during pregnancy are scarce although they represent a therapy of considerable interest for effectiveness and manageability.

Aim: To evaluate data of efficacy and safety of TPO-RA in pregnant women with ITP in 7 Italian centers.
Methods: Retrospective collection data from hospital charts, including ITP history, previous therapies, type and dosage of TPO-RA, duration of therapy with TPO-RA, platelet count at delivery , thrombotic, hemorrhagic and other adverse events, maternal and fetal outcome.
Results: We recorded data of 13 women, 16 pregnacies and 17 newborns (one twin pregnancy), summarized in Table 1. Median age at delivery was 33 yrs (22-46). 3 patients had a de novo ITP while in 13 pregnancies a chronic ITP was already known with a median disease duration of 12 years (1-41). Median n of previous lines of therapy before pregnancy was 3 (0-6); these included 4 splenectomy, while 7 patients had received TPO-RA before index pregnancy. All patients received TPO-RA during pregnancy for steroid refractoriness. Median plt count at TPO-RA start was 29 x 10e9/L Romiplostim (median weekly dose 6 mcg/Kg) and Eltrombopag (median daily dose 25 mg) were administered in 10 and 6 patients respectively for a median of 33 days (5-280) before delivery. The limited number of treated patients makes any reference to a different efficacy of the two TPO-RA not reliable. In 11 cases TPO-RA were combined: with Steroids (7), Steroid plus IVIG (1), IVIG (2) Steroid and cyclosporine A (1). In 6 pregnancies mucocutaneus bleeding were reported (all WHO 1 grade) and resolved after the use of TPO-RA. ORR to TPO-RA was 100% (11 Complete response, 5 Response) and the median platelet count at delivery was 112 x10e9/L (58-250). No thrombotic, nor other complications were reported. Cesarean section was performed in 5 deliveries (31%) and only in one case of vaginal delivery a peripartum bleeding occurred (WHO 2 grade). There was only one case of premature delivery due to placenta previa with a planned cesarean section without relevant bleeding (WHO 1 grade). 10 newborns (59%) presented thrombocytopenia (plt <50 x 10e9/L) at birth and were treated with IVIG in combination or alone with plt transfusion, with complete resolution. Figure 1 shows maternal plt count at different time

point and their related newborn platelet count at birth. In 13 mothers (81%) TPO-RA therapy was continued after delivery. 6/12 known neonates received breast-feeding concomitantly with ITP treatment received after delivery.

Conclusions: For patients with ITP during pregnancy, data on the efficacy and safety of other therapies besides S and IVIG are scarce. In our case series TPO-RA therapy appears safe, manageable and effective to increase platelet count for delivery in patients with chronic, S-refractory disease. No thrombotic events nor specific complications for newborns were reported. These positive and encouraging data require confirmation in larger series.

Table 1.

Characteristics of patients

ITP phase during pregnancy – no. (%) N=16	
De novo	3 (19)
Chronic	13 (81)
Median age at delivery (range) -yr	33 (22-46)
Median duration of ITP (range) - yr	12 (0-41)
Median no. of previous ITP therapies (range)	3 (0-6)
Previous splenectomy – no. (%)	4 (30)
TPO-RA pre-pregnancy – no. (%)	7 (53)
Romiplostin - no. pregnancy (%)	10 (62)
Eltrombopag - no. pregnancy (%)	6 (38)
Romiplostim median dose (range)	6 mcg/Kg (1-10)
Eltrombopag median dose (range)	25 mg/die (25-50)
Median duration of TPO-RA therapy (range) - days	33 (5-280)
Concomitant therapies with TPO-RA – no. (%)	Steroid 7 (44) IVIG 2 (12) Steroid+IVIG 1 (6) Steroid+CSA 1 (6) TPO alone 5 (32)
TPO-RA therapy ORR – no. (%)	16 (100)
CR	11 (69)
PR	5 (31)
Median platelet count at delivery (range) – x10e9/L	112 (58-250)
Cesarean section – no. (%)	5 (31)
Peripartum bleeding - no. (%)	1 (6)
Thrombosis during TPO-RA treatment – no. (%)	0 (0)
Bleeding during TPO-RA treatment – no. (%)	0 (0)
Other adverse events during TPO-RA treatment – no. (%)	0 (0)
Thrombocytopenic newborns no. (%)	10 (58)
Treatment of thrombocytopenic neonates (no. = 10)	
IVIG alone – no (%)	3 (30)
Platelet transfusion + IVIG – no (%)	7 (70)
Breastfeeded neonates (out of 12 known)	6/12

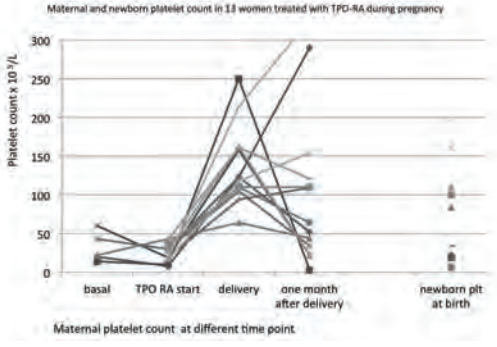

Figure 1.

CO014

SAFETY AND EFFICACY OF EFGARTIGIMOD IN PRIMARY IMMUNE THROMBOCYTOPENIA: ADVANCE IV+ 2-YEAR ANALYSIS

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Background and Aims: Efgartigimod (EFG), a human IgG1 antibody Fc fragment, blocks the neonatal Fc receptor (FcRn), decreasing IgG recycling, including pathogenic autoantibodies that cause primary immune thrombocytopenia (ITP). Intravenous (IV) EFG was evaluated in the phase 3 ADVANCE IV trial (NCT04188379) in 131 adults with long standing ITP. Participants could roll over to the open-label extension trial, ADVANCE IV+, which assessed the long-term safety and efficacy of EFG.

Methods: EFG (10 mg/kg IV) was administered weekly or every-other-week as per ADVANCE IV. The dosing regimen could be adjusted according to platelet count response. The primary endpoint was the frequency and severity of adverse events (AEs), as well as vital signs and laboratory assessments.

Results: As of September 2023, 101 participants entered ADVANCE IV+. 48.5% and 34.1% completed the first and second 52-week treatment periods, respectively, and 34.7% were ongoing at the clinical cut-off date. 57.4% (n=58) discontinued the study, mostly due to consent withdrawal (n=26) and lack of efficacy (n=23). Mean (SD) number of EFG infusions was 38.8 (31.6); 33.7% received every-other-week dosing (stable platelet count [PC] $\geq 100\times10^9$/L) at any time. In the placebo–EFG group (n=38), 26.3% had sustained PC responses ($\geq 50\times10^9$/L) at ≥4 visits between weeks 19–24 of the first 52 weeks; 23.7% achieved a PC of $\geq 50\times10^9$/L in ≥4 of the first 6 weeks. Mean (SD) percentage of weeks with a PC of $\geq 50\times10^9$/L for the total EFG group was 39.2% (38.8). 92.1% (event rate [ER] 6.76) and 11.9% (ER 0.24) of patients experienced AEs and treatment-related AEs, respectively. Most AEs were mild/moderate in severity (serious AEs: 15.8% [ER

0.24]; infections: 37.6% [ER 0.76]; deaths: n=3); no serious AEs or deaths were treatment-related.
Conclusions: Long-term EFG treatment in participants with long-standing ITP was well tolerated and demonstrated sustained PC increases. Participants switching from placebo to EFG had early PC increases.

CO015

THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RAS): A PROMISING THERAPY FOR CHEMOTHERAPY INDUCED THROMBOCYTOPENIA (CIT)

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Background and Aims: Chemotherapy-induced thrombocytopenia (CIT) is an often-underestimated complication of some oncologic treatments. CIT affects approximately one-third of patients with solid tumor and contributes to morbidity and mortality due to hemorrhagic events. A platelet count below 100×10^9/L is often managed with reduction of therapy relative dose intensity (RDI), influencing oncologic outcomes and patients' psychological well-being. The use of thrombopoietin receptor agonists (TPO-RAs) in managing CIT aims to stimulate bone marrow megakaryocytopoiesis, therefore increasing platelet production. The efficacy of TPO-RAs in treating and preventing CIT is still a matter of debate in the scientific community. Our purpose was to evaluate the efficacy of TPO-RAs in treating CIT, particularly in increasing platelet count. We also wanted to assess their safety profile, especially regarding thrombotic events.
Methods: We included 13 oncologic patients with a diagnosis of CIT and treated off-label with TPO-RAs in the hematology centre of Policlinico Umberto I – Sapienza University of Rome. All subjects signed an informed consent for therapy and for scientific purposes. Data were retrospectively collected through an "ad hoc" CRF. Follow-up was calculated since TPO-RAs start to the last visit.
Results: The characteristics of patient population are listed in Figure 1a. All the patients presented with a platelet count $<100\times10^9$/L, which was considered by oncologists a hindrance in complying with proper cancer therapy. Nine subjects (69%) received only chemotherapy while 4 (31%) chemotherapy plus immunotherapy. The pie chart shows cancer types by anatomical site of origin (Figure 1b). The entire cohort firstly underwent treatment with corticosteroids; no one obtained a full persistent response in platelet number with a median maximum platelet count (MMPC) of 58×10^9/L, (IQR 38×10^9/L); no one of them was able to receive further cancer treatment. In 7/13 cases (54%) a bone marrow biopsy was performed before starting the administration of TPO-RAs, while 6/13 (46%) had undergone a bone marrow aspirate. Two cases (15%) presented evidence of metastatic bone marrow involvement. Six patients (46%) were treated with Romiplostim and 7 (54%) with Eltrombopag. The median time of treatment was 6 months (IQR 12). Twelve/13 (92%) achieved a platelet count $>100\times10^9$/L in a median time of 14 days (IQR 10); 1/13 (8%) doubled his initial platelet count obtaining a value of 70×10^9/L. All patients maintained a persistent platelet response and were able to correctly attend oncologic treatments. Moreover, 3 (23%) were even able to discontinue TPO-RAs administration. MMPC reached during TPO-RAs was 244×10^9/L (IQR 161×10^9/L); median follow-up was 7 months (IQR 10). At last visit, the median platelet value was 133×10^9/L (IQR 114×10^9/L). No thrombotic complications were observed. At the time of data collection, 3 subjects were deceased due to infection or cancer progression.
Conclusions: Our results demonstrated a good efficacy, tolerance and safety of TPO-RAs in CIT. Furthermore, being able to undergo anticancer therapy without RDI reduction is crucial for both the neoplastic outcome and psychological well-being of the patients. The management of CIT remains an unmet clinical need. TPO-RAs could represent a promising option although further studies on larger cohorts are necessary.

Characteristics	Total N=13
Male sex – no. (%)	7 (54)
Female sex – no. (%)	6 (46)
Previous ITP diagnosis – no. (%)	4 (31)
Bone marrow (BM) assessment – no. (%)	
Biopsy	7 (54)
Aspirate	6 (46)
BM metastatic involvement – no. (%)	2 (15)
Metastatic cancer – no. (%)	7 (54)
Age (yrs) at TPO-RA start – Median (IQR)	55 (53-69)
TPO-RA treatment (mths) – Median (IQR)	6 (4-16)
Follow-up (mths) – Median (IQR)	7 (4-14)

Figure 1a

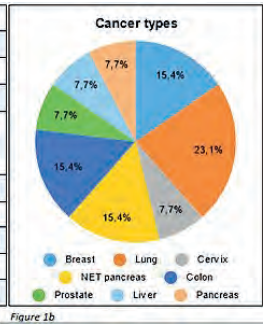

Figure 1b

Figure 1.

CO016

ITALIAN REGISTRY ON ACTIVE ADULT IMMUNE THROMBOCYTOPENIA (ITP) - GIMEMA ITP0918 STUDY: A GENERAL SNAPSHOT WITH A FOCUS ON TREATMENTS BEFORE AND AFTER THE INTRODUCTION OF TPO-RA AND ON THROMBOTIC EVENTS

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Background: Registry studies are an important source of real-world clinical and patient-reported data. Italian Registry on active adult ITP aims to produce a dynamic picture of disease natural history and therapeutic management of patients. This analysis focused on therapeutic choices analyzed by ITP phase and on thrombotic events.
Methods: From October 2018 to April 2024 26 hematological centers in Italy joined the Registry, sequentially recruiting adults with primary ITP (pITP) on active treatment at the time of enrollment: initiating a 1st line (group A) or modifying a previous treatment (group B) or on ongoing treatment (group C). Historical data are retrospectively collected at study entry and prospectively at annual visits, using REDCap. The study is sponsored by GIMEMA Foundation (Rome). Data collection and analysis are performed by Hematology Project Foundation (Vicenza).
Results: On April 15, 2024, 971 patients (pts) were recruited, of which 892 were evaluable for the analysis: 130 (14.6%) in group A and 762 (85.4%) in group B+C. Median time from diagnosis to enrollment was 3.9 yrs. Median age at diagnosis and at enrollment was 52 and 62 yrs respectively. Male were 384 (43%) and female were 508 (57%). Median platelet count was $95x10^9$/L at enrollment and $19x10^9$/L at diagnosis. At entry, 152 (91 A and 61 B+C) patients were newly diagnosed ITP, approximately 40% of whom required a 2nd line therapy; in these patients, most common 2nd line therapy was eltrombopag (57%), followed by romiplostim (18%) and rituximab (12%). 93 and 647 patients were in persistent or chronic phase of ITP at baseline, respectively. Median duration of ITP at study entry was 7 mo for persistent ITP patients and 81 mo for chronic ones. Median previous lines of therapy was 2. In patients treated before 2010, most prescribed 2nd line treatment was splenectomy (53%) followed by rituximab (25%) and azathioprine (9%). In those diagnosed after 2010, most prescribed 2nd line treatment was eltrombopag (62%) followed by romiplostim (14%) and rituximab (9%). Splenectomy was performed in 118 (12%) patients, 55 (47%) before 2010 and 63 (53%) after 2010 (23 in the last 5 yrs). At the enrollment in the Registry 69 patients (8%) experienced past arterial (33 pts), venous (32 pts) thrombosis or both (4 pts). Prevalence of thrombosis was 12.5% and 4.1% for male and female, respectively with a ratio of arterial/venous events of 1.4/1 for male and 1/2 for female. The most frequent arterial event in male was acute myocardial infarction followed by stroke while in female was TIA followed by acute myocardial infarction. Venous events were mostly unprovoked (80%). Deep vein thrombosis was the most frequent venous event (56%) followed by pulmonary embolism (19%). Two cases of cerebral thrombosis and one case of splanchnic thrombosis were reported.
Conclusions: The Italian ITP Registry represents the most important experience of real-life multicenter data in Italy on adult patients with active ITP. It captured the change in therapy management, highlighting an increasingly early use of TPO-RA. Splenectomy emerges as a valid therapeutic option still used in current clinical practice. From this ad interim analysis emerges that a significant proportion of ITP patients experienced thrombosis, an important issue with impact on treatment choice and management.

CO017

THE ROLE OF FOSTAMATINIB IN ITP PATIENTS WITH HIGH THROMBOTIC RISK: AN ITALIAN MULTICENTER EXPERIENCE

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Background and Aims: Patients with immune thrombocytopenia (ITP) face approximately twice the risk of developing thrombosis compared to the general population. The risk increases further in patients treated with thrombopoietin agonists. However, fostamatinib, due to its distinct mechanism of action, appears to be safe from an increased risk of thrombosis and is therefore deemed preferable for ITP patients with high thrombotic risk. This study aims to evaluate the safety and effectiveness of fostamatinib in ITP patients with a heightened risk of thrombosis.

Methods: We conducted a retrospective study at three specialized medical centers in Italy, namely Policlinico Gemelli IRCCS in Rome, Azienda Ospedaliero Universitaria Careggi in Florence, and ASST Fatebenefratelli-Sacco in Milan. The study focused on ITP patients at high risk of thrombosis who were treated with fostamatinib. Patients were classified at high risk for thrombosis if they had previously experienced thrombosis, or if they tested positive for medium to high titer antiphospholipid antibodies (APLAs) or other thrombophilic conditions. The primary endpoint of the study was to determine the rate of thrombotic events, while secondary endpoints included the response rate and adverse events.

Results: Out of the total 57 patients treated with fostamatinib as of February 2024, 30 patients (15 males and 15 females) were at high risk of thrombosis. The clinical characteristics of this group were presented in Table 1. Among them, 17 patients (56.7%) had a personal history of thrombosis, with 11 (36.7%) experiencing arterial events and 8 (26.7%) experiencing venous events. Two patients had both arterial and venous events, while two others had recurrent cardiovascular events. A thrombophilic condition was present in 17 patients (56.7%), with 14 (46.7%) testing positive for antiphospholipid antibodies (APLAs). Two patients (6.7%) had a previous diagnosis of secondary myelofibrosis (MF); one of them tested positive for APLAs. Inherited thrombophilia was present in 3 patients (10.0%): one with a protein S (PS) deficiency, one with FV Leiden heterozygosity, and one with PT G20210A heterozygosity. Only four patients (13.3%) had both a previous thrombotic event and a thrombophilic condition (PS deficiency=1, APLA=1, APLA+heterozygous PT20210A=1, MF+APLA=1) . Concomitant use of antithrombotic drugs was recorded in 12 patients (40.0%). The total observation time was 14 years, median 4.6 months (range 17 days – 1.2 years), and no thrombotic events were recorded during this period. A response (platelet count ≥30,000/ μL) was observed in 24 patients, resulting in an overall response rate of 80.0% (range 30,000 to 290,000), with 10 patients (33.3%) achieving a complete response with a platelet count ≥100,000/μL. Thirteen patients (43.3%) experienced an adverse event, including gastrointestinal symptoms (n=9, 6.7%), increased liver enzymes (n=3, 10%), and hypertension (n=2, 6.7%). The main cause of discontinuation was lack of efficacy (n=8, 26.7%), and only 6 patients (20.0%) discontinued fostamatinib due to intolerance.

Conclusions: Managing ITP patients at high risk of thrombotic events poses a significant challenge. Despite severe thrombocytopenia, these patients often encounter thrombotic events, and many require a safe platelet count to receive appropriate antithrombotic therapy. In our cohort, fostamatinib demonstrated effectiveness in achieving a safe platelet count in 80% of patients, with no documented thrombotic events during the observation period.

Table 1.

Clinical characteristics	N (%)
Male	**15 (50%)**
Age at diagnosis - median (range)	**55 (2-79)**
Platelet count at diagnosis- median (range)	**13 (1-70)**
Prior treatment lines – median (range)	**3 (1-9)**
Steroids	*30 (100%)*
IgHD	*8 (26.7%)*
TPO-RAs	*16 (53.3%)*
Rituximab	*7 (23.3%)*
Immunosuppressant agents	*6 (20%)*
Splenectomy	*4 (13.3%)*
Age at fostamatinib – median (range)	**1 (3.3%)**
Platelet count at fostamatinib – median (range)	**2 (6.7%)**
Concomitant treatments	**17 (56.7%)**
Steroids	*10 (33.3%)*
IgHD	*3 (10%)*
Rituximab	*1 (3.3%)*
Immunosuppressant agents	*5 (16.7%)*
Previous thrombosis	**17 (56.7%)**
Venous thrombosis	**8 (26.7%)**
Deep vein thrombosis	*5 (16.7%)*
Pulmonary embolism	*1 (3.3%)*
Deep vein thrombosis/pulmonary embolism	*2 (6.7%)*
Arterial thrombosis	**11 (36.7%)**
Acute coronary syndrome	*7 (23.3%)*
Cerebrovascular accident	*3 (10.0%)*
Peripheral arteriopathy	*1 (3.3%)*
Thrombophilia	**17 (56.7%)**
Antiphospholipids	*14 (46.7%)*
FV Leiden	*1 (3.3%)*
PTG20210A	*1 (3.3%)*
Protein S deficiency	*1 (3.3%)*
Myeloproliferative neoplasms	*2 (6.7%)*

CO018
ADOPT PHASE 4 STUDY: INTERIM ANALYSIS OF THE EFFICACY AND SAFETY RESULTS OF AVATROMBOPAG TREATMENT IN ADULT PATIENTS WITH IMMUNE THROMBOCYTOPENIA

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Background and Aims: Avatrombopag (AVA) is a thrombopoietin receptor agonist approved for the treatment of chronic immune thrombocytopenia (ITP) in adult patients (pts) refractory to other therapies. AVA is administered orally with no dietary restrictions and no significant hepatotoxicity.The ADOPT study (NCT04943042) in Europe evaluates AVA's real-world effectiveness in routine clinical practice. This first interim analysis describes the efficacy and safety results of the ADOPT study.

Methods: The study collects both retrospective and prospective data. over a 12-month period. Eligible patients must be ≥18 years of age with a diagnosis of ITP. Exclusion criteria include enrollment in other interventional clinical trials or use of an investigational drug ≤3 months prior to enrollment. The primary endpoint is the cumulative number of weeks with a platelet count (PC) $\geq 30\times10^9$/L. Secondary endpoints include the cumulative number of weeks with a PC$\geq 50\times10^9$/L, pts with a PC$\geq 30\times10^9$/L and $\geq 50\times10^9$/L for at least 8 consecutive weeks, pts with WHO bleeding grade ≥2, pts requiring rescue medication, and time from AVA initiation to PC$\geq 30\times10^9$/L and $\geq 50\times10^9$/L. Safety endpoints include serious adverse events (SAEs) and adverse events of special interest (AESIs; thromboembolic events [TEEs] and major bleeding events).

Results: The study completed enrollment in Jan 2024, with 200 pts recruited at 51 centers in Europe. As of 2 Jan 2024, 7 pts completed the 12-month study period. The cumulative median (mix, max) number of weeks with PC$\geq 30\times10^9$/L was 51.3 (45.4, 61.1),all 7 pts achieved PC ≥30 and $\geq 50\times10^9$/L for at least 8 consecutive weeks. Baseline characteristics and post-treatment safety information were available for 147 pts (Table 1), 31 (21.1%) pts had newly diagnosed/persistent ITP with ≤12 months of disease duration since diagnosis; 116 (78.9%) had chronic ITP. 84 (57.1%) had no prior exposure to TPO-RAs. 20 pts reported 41 AEs since the start of treatment, among these AEs 7 were AVA-related. One non-treatment-related death occurred. There were 6 AESIs, including 4 TEEs, none of which were considered AVA-related or led to treatment discontinuation (Table 1).

Conclusions: This first interim analysis suggests that AVA efficacy and safety in European routine practice align with the clinical trial program. These data support AVA real world effectiveness even in patient subgroups not previously included in the clinical program (newly diagnosed/persistent ITP, prior TEEs).

Table 1.

Interim Baseline Characteristics and Efficacy and Safety and Outcomes

Interim Baseline Characteristics Full analysis set	Avatrombopag N = 147
Age (years)	
Mean (SD)	54.4 (18.4)
Median (Min, Max)	55.0 (18, 92)
Gender, n (%)	
Male	65 (44.2)
Female	82 (55.8)
Time since ITP diagnosis to first AVA treatment (weeks)	
Mean (SD)	469.2 (614.4)[a]
Median (Min, Max)	271.6 (0.1, 3 389.7)[b]
Time since ITP diagnosis to first AVA treatment, n (%)	
≤ 12 months	31 (21.1)
> 12 months	116 (78.9)
Platelet count prior to first AVA treatment, n (%)	
<30	54 (36.7)
30 – 50	24 (16.3)
≥50	57 (38.8)
Missing	12 (8.2)
Previous treatment with a TPO-RA within 12 months prior to AVA treatment start, n (%)[c]	
Yes	63 (42.9)
Eltrombopag	31 (21.1)
Romiplostim	40 (27.2)
No	84 (57.1)
Previous treatment with corticosteroids within 12 months prior to AVA treatment start, n (%)[c]	
Yes	45 (30.6)
Prednisolone	34 (23.1)
Dexamethasone	19 (12.9)
No	102 (69.4)
Other previous ITP treatments within 12 months prior to AVA treatment start, n (%)[c]	
IVIg	20 (13.6)
Rituximab	2 (1.4)
Fostamatinib	8 (5.4)
Splenectomy status, n (%)	
Yes	12 (8.2)
No	135 (91.8)
History of thromboembolic events, n (%)	
Yes	16 (10.9)
Venous	8
Arterial	8
No	131 (89.1)
Previous major bleeding events	
Yes	13 (8.8)
No	134 (91.2)
Interim Efficacy Outcomes **Enrollment to 12-month Period**	**Avatrombopag** **N = 7**
Cumulative Number of Weeks with a PC≥30×10⁹/L	
Mean (SD)	52.2 (5.5)
Median (min, max)	51.3 (45.4, 61.1)
Patients with at least 8 weeks of data in the analysis period with a PC≥30×10⁹/L, n (%)	7 (100)
Patients with a platelet count ≥30×10⁹/L, for at least 8 consecutive weeks, n (%)	7 (100)
Cumulative Number of Weeks with a PC≥50×10⁹/L	
Mean (SD)	48.1 (7.2)
Median (min, max)	47.0 (38.1, 61.1)
Patients with a platelet count ≥50×10⁹/L, for at least 8 consecutive weeks, n (%)	7 (100)
Patients requiring rescue medication, n (%)	2 (28.6)
Patients experiencing WHO bleeding grade ≥2, n (%)	0
Interim Safety Outcomes since treatment initiation **Full analysis set**	**Avatrombopag** **N = 147**
All AEs, n (%) [e]	20 (13.6) [41]
AEs related to AVA	6 (4.1) [7]
AEs that result in discontinuation of AVA	1 (0.7) [2]
Patients with at least one SAE	11 (7.5) [15]
AESIs	5 (3.4) [6]

[a]Mean (SD) reported as 3284.7 (4300.8) days. [b]Median (Min, Max) reported as 1901.0 (1, 23728) days. [c]Subjects with multiple reported medications are counted once at each medication category

CO019
MACHINE LEARNING APPROACH FOR PREDICTION OF OUTCOMES IN ANTICOAGULATED PATIENTS WITH ATRIAL FIBRILLATION

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Background: Despite the availability of different risk scores, the accuracy of actual prediction tools for outcomes in patients with atrial fibrillation (AF) remains modest. Although Machine Learning (ML) has been used to predict outcomes in the AF population, evidences about outcome prediction in a population entirely on oral anticoagulation is lacking. The aim of this study is to use ML to predict outcomes in anticoagulated patients with atrial fibrillation, processing data from the Italian AF START-2 Register.
Methods and Aims: Different ML models were applied to predict all-cause death, cardiovascular (CV) death, major bleeding and stroke in anticoagulated patients with nonvalvular AF. Overall population, Vitamin K Antagonists (VKA) and Direct Oral Anticoagulants (DOACs) populations were considered for the analyses.
Results: 11078 AF patients (male n=6029, 54.3%) were enrolled with a median follow-up period of 1.5 years [IQR 1.0-2.6]. Patients on VKA were 5135 (46.4%), while 5943 (53.6%) were on DOACs. During the follow-up, 785 patients died, of which 169 (21.6%) due to CV causes; 240 major bleeding events were recorded, and 50 strokes occurred. Using Multi-Gate Mixture of Experts (MmoE), a cross-validated AUC of 0.779±0.016 and 0.745±0.022 were obtained, respectively, for the prediction of all-cause death and CV death in the overall population. The best ML model outperformed CHA2DS-VA2SC and HAS-BLED for all-cause death prediction (p<0.001 for both). When compared to HAS-BLED, Gradient Boosting improved major bleeding prediction in DOACs patients compared to HAS-BLED score (0.711 *vs.* 0.586, p<0.001). Body mass index, age, glomerular filtration rate, platelet count and hemoglobin levels resulted the most important variables for ML prediction (Figure 1).

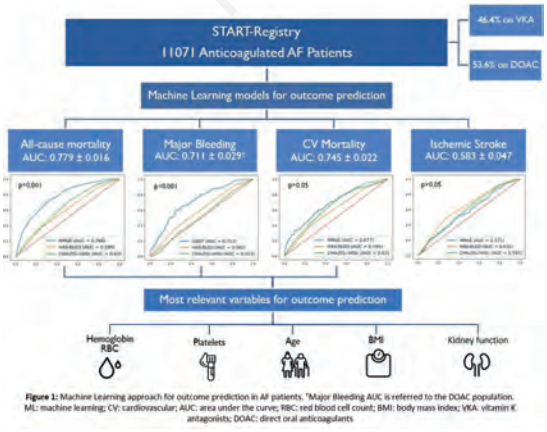

Figure 1.

Conclusions: In patients with AF, ML models showed good discriminative ability to predict all-cause death, regardless of the type of anticoagulation strategy, and major bleeding on DOAC therapy, outperforming CHA2DS2-VASC and the HAS-BLED scores for risk prediction in these populations. Anemia, platelet count, and BMI emerged as new potential risk predictors in anticoagulated AF patients. The applications of ML prediction models in clinical practice could improve the risk assessment and subsequent management of anticoagulated patients with AF.

CO020

PROGNOSTIC ROLE OF D-DIMER IN PATIENTS WITH ATRIAL FIBRILLATION AND CONCOMITANT PCI ON DUAL OR TRIPLE ANTITHROMBOTIC THERAPY

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Background: Antithrombotic management of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) can be challenging. Recent direct oral anticoagulant (DOAC) trials demonstrated the safety of double antithrombotic therapy (DAT) in comparison with triple antithrombotic therapy (TAT) in this setting. However, this benefit is counterbalanced by a higher risk of ischemic, mainly stent-related, events. Several clinical studies have suggested a crucial role for oxidative stress in increasing the thrombotic risk in patients affected from cardiovascular diseases.
Objectives: We sought to identify the possible clinical relevance of D-dimer (DD) in a real-world population with concomitant AF and PCI.
Methods: All consecutive patients with history of AF discharged from our cardiology ward with DAT or TAT after a PCI from April 2018 to March 2021 were enrolled in an observational registry. For all subjects, blood EDTA samples were collected, and DD plasma concentrations were assessed by using a commercial kit (VIDAS® D-Dimer). Major adverse cardiac and cerebrovascular events (MACCE) and major hemorrhagic or clinically relevant non major bleeding events together with therapeutic changes were recorded at 3 and 12-months follow-up.
Results: A total of 147 patients were included (70.1% after acute coronary syndromes-ACS). Ninety-one patients (62%) were discharged with TAT. Both in TAT and in DAT group DOACs were preferred (58% and 77%, respectively). In 93.4% of patients, clopidogrel was chosen as P2Y12 inhibitor. The median follow-up was 401 days (IQR 241-588). MACCE occurred in 22 cases

(15.0%), while hemorrhagic events in 19 (12.9%), 14 of which were major (9.5%), with no significant differences between TAT and DAT group. The incidence of all-cause death was 11.6%. DD levels did not differ between patients in TAT and in DAT groups. DD levels were significantly higher in patients who experienced a MACCE at follow-up (1412, IQR 872-2878, *vs* 882 IQR 496-1618, p=0.021). At multivariate Cox regression analysis after adjustment for the potential confounders, DD values were significantly associated with the occurrence of MACCE [HR variation 1.34 (1.03-1.75), p=0.03], hemorrhagic events [HR 1.64 (1.13-2.38), p=0.011] and all-cause mortality [HR 1.72 (1.13-2.61), p=0.011].

Conclusions: In a real-world unselected population, a significant incidence of ischemic as well as hemorrhagic events was observed both in patients on TAT and DAT early after discharge. Our data documented a significant prognostic role of DD for both ischemic and hemorrhagic events as well as all-cause mortality, independently from cardiovascular risk factors, clinical presentation and antithrombotic therapy.

CO021

PATIENTS WITH SUDDEN SENSORINEURAL HEARING LOSS HAVE A HIGH PREVALENCE OF RIGHT-TO-LEFT SHUNT AND HIGHER PREVALENCE OF PATENT FORAMEN OVALE WHEN COMPARED TO GENERAL HEALTHY POPULATION

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Background and Aims: Sudden sensorineural hearing loss (SSNHL) is a 30 dB hearing loss over at least 3 contiguous frequencies occurring within 3 days. It is mostly classified as idiopathic, though inflammatory and vascular compromise of the inner ear have been reported. A possible cause of SSNHL is represented by paradoxical micro-embolization due to right-to-left shunt (RLS), most frequently in case of patent foramen ovale (PFO). It has been postulated that patients with SSNHL have a higher prevalence of PFO compared to the healthy adult population (***i.e.***, 15-25%). We investigated the prevalence of RLS, PFO and co-existing major cardiovascular and thrombophilic risk factors in patients suffering from SSNHL.

Methods: We conducted a retrospective study on a cohort of patients with a diagnosis of idiopathic SSNHL following ear-nose-throat (ENT) examination. Clinical data and blood samples were collected to investigate cardiovascular and thrombophilic risk factors, while RLS/PFO was detected either through contrast-enhanced transcranial Doppler ultrasound (C-TCD), contrast-enhanced transthoracic echocardiography (C-TTE) or transesophageal echocardiography (TEE). Data from brain MRI were also included whenever available.

Results: We included 228 patients, of whom 142/228 (62%) were screened for RLS; in particular, C-TCD was performed in 29/142 (20%), C-TTE in 64/142 (45%), and TEE in 49/142 (34.5%). C-TCD was positive in 13/29 patients (45%), C-TTE in 27/64 (42%), TEE in 23/49 (47%), allowing us to detect RLS in 63/142 patients (44.4%). Thus, the prevalence of PFO in our cohort of patients with SSNHL was 50/114 (43.9%), which is significantly higher than what is known in the general healthy population (p <0.001). We investigated additional potential risk factors, according to the presence of RLS (as seen in Table 1). No difference was seen in terms of age and sex. Prevalence of thrombophilic risk factors investigated were similar, except for a higher prevalence of heterozygosity for FV Leiden in the group with RLS [6/39 (15.4%)] compared to the counterpart [1/52 (1.9%)]. Cardiovascular risk factors were also equally distributed among the two groups, but with a lower prevalence of systemic arterial hypertension in patients with RLS [7/59 (11.9%)] compared to those without RLS [20/74 (27%)]. Furthermore, our analysis shown a slightly higher prevalence of ischemic signs in patient with RLS than in those without RLS.

Table 1.

Thrombophilic and cardiovascular risk factor according to presence pf RLS in SSNHL population.

	non RLS (n = 72/127, 56.7%)	RLS (n = 55/127, 43.3%)
Female (n,%)	41/71 (57.7%)	31/49 (63.2%)
Age [years (SD)]	46 (13)	48 (11)
Hyperfibrinogenemia (n,%)	2/58 (3.4%)	1/35 (2.8%)
Protein S deficiency (n,%)	1/59 (1.7%)	0/36 (0%)
Protein C deficiency (n,%)	0/59 (0%)	0/37 (0%)
Antithrombin deficiency (n,%)	0/57 (0%)	0/37 (0%)
Elevated homocysteine (n,%)	9/60 (15%)	6/35 (17%)
Elevated RAPC (n,%)	5/51 (9.8%)	5/29 (17%)
Heterozygosity for FV Leiden (n,%)	1/52 (1.9%)	6/39 (15.4%)
FII polymorphism (n,%)	3/54 (5.5%)	2/33 (6%)
Factor XII deficiency (n,%)	3/46 (6.5%)	2/25 (8%)
Elevated Factor VII (n,%)	8/51(15.7%)	8/31 (25.8%)
Elevated Factor VIII (n,%)	7/55 (12.7%)	5/34 (14.7%)
Antiphospholipid antibodies (n,%)	1/55 (1.8%)	2/36 (5.5%)
Systemic arterial hypertension (n,%)	20/74 (27%)	7/59 (11.9%)
Diabetes Mellitus (n,%)	3/65 (4.6%)	2/46 (4.3%)
Dyslipidemia (n,%)	18/67 (26.8%)	15/45 (33.3%)
Smoking (ever) (n,%)	12/65 (3%)	9/43 (9.3%)
Overweight (n,%)	9/60 (15%)	6/38 (15.7%)
Personal history CV events (n,%)	2/48 (4.1%)	2/35 (5.7%)
Personal history thromboembolic events (n,%)	3/48 (6.25%)	1/35 (2.9%)
Familial history CV events (n,%)	27/63 (42.8%)	15/44 (34%)
Familial history thromboembolic events (n,%)	2/63 (3.17%)	4/44 (9%)
Encephalic MRI positive for ischemic signs (n,%)	15/67 (22%)	21/53 (39.6%)

Conclusions: We report a prevalence of RLS exceeding 40% in patients with SSNHL. We also demonstrate that PFO is more represented in this patient subset compared to the general population, in which it has been reported in up to 25% subjects. Thus, RLS assessment should be considered as part of the evaluation in patients with SSNHL. This association may suggest that either paradoxical embolism, such as a venous embolism through of PFO, or *in situ* clot could be the cause of SSNHL in a proportion of patients previously labelled as 'idiopathic'. Moreover, we report that the

prevalence of FV Leiden is slightly higher in patients having RLS, while such trend is not observed for major cardiovascular risk factors. Our hypothesis warrants confirmation in larger cohorts because of the potential to early identify and properly treat patients at risk for further and more severe ischemic complications.

CO022

LEFT ATRIAL ENLARGEMENT IS AN INDEPENDENT PREDICTOR OF CEREBROVASCULAR EVENTS IN PATIENTS WITHOUT ATRIAL FIBRILLATION: PRELIMINARY RESULTS FROM AN OBSERVATIONAL COHORT STUDY BASED ON ADMINISTRATIVE DATABASES

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Background and Aims: Left atrial enlargement (LAE) is a known risk factor for the development of atrial fibrillation (AF). However, it is currently unclear if LAE is an independent risk factor for stroke in patients without AF. LA cardiopathy is one of the putative pathomechanisms of embolic stroke of unknown source (ESUS), a subtype of cryptogenic stroke which is deemed to be secondary to embolism in the absence of a major cardiac source. With this study, we aimed to assess the frequency of 1-year cerebrovascular events in patients with different degrees of LAE, evaluated with the Left Atrial Volume Index (LAVi).

Methods: In this observational, retrospective cohort study, we screened all subjects over 18 years of age residing in the Metropolitan Area of Milan who had an echocardiogram performed between 2010 and 2023 at university hospitals in Milan. We included subjects for whom record linkage with administrative databases maintained by the Metropolitan Area of Milan was possible and for whom the LAVi was available. Only the first echocardiogram for each solar year (index echocardiogram, IE) was included in the analysis. We excluded subjects if the 1-year follow-up (FU) after the IE was incomplete; if the patient died before the completion of the 1-year FU; if AF was known at the time of the IE; or if there was evidence of ongoing anticoagulant therapy up to 4 months prior or 1 year after the IE. Record linkage was performed to collect data regarding the eligible patients' comorbidities and primary outcome events (stroke or transient ischemic attack – TIA – within 1 year since the IE).

Results: In this preliminary analysis we included 53109 adult subjects. Their median age was 66 years (IQR, 53-76); 25278 (47.6%) were female. The most frequent comorbidities were arterial hypertension (49.4%) and diabetes mellitus (DM) (14.4%); 7% of patients had a history of stroke. Based on the results of the IE, 39147 subjects (73.7%) had a normal LAVi (<35 mL/m2), 7103 (13.4%) had mild LAE (35-42 mL/m2), 3065 (5.8%) had moderate LAE (42-48 mL/m2), and 3794 (7.1%) had severe LAE (>48 mL/m2). Within 1 year since the IE, 1318 subjects (2.5%) developed a primary outcome event (ischemic stroke or TIA). The frequency of the primary outcome event increased with increasing degrees of LAE, as it was 2.0% in subjects with a normal LAVi, and 3.0%, 4.1% and 5.3% in patients with mild, moderate, and severe LAE, respectively. The effect size of severe LAE was greater in females [OR 3.92 (95% CI, 3.1-4.9) *vs* 2.07 (95% CI, 1.7-2.6) in males], in subjects without hypertension [3.16 (95% CI, 2.3-4.3) *vs* 2.26 (95% CI, 1.9-2.7) in hypertensive subjects], in subjects without DM [OR 2.89 (95% CI, 2.4-3.5) *vs* 2.03 (95% CI, 1.5-2.8) in diabetic subjects), and in subjects with no prior stroke [OR 3.09 (95% CI, 2.5-3.8) *vs* 1.60 (95% CI, 1.1-2.1) in patients with a history of stroke]. Similar trends were noted also among patients with moderate LAE.

Conclusions: The 1-year risk of ischemic stroke or TIA increases with the degree of LAE. Interestingly, this association is greater in patients who would not be considered at heightened cardiovascular risk according to traditional risk factors. Further research is needed to explore the implications of these findings in clinical practice.

CO023

INAPPROPRIATE UNDERDOSING OF DIRECT ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION PATIENTS: RESULTS FROM THE START2-AF REGISTRY

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Background and Aims: Direct oral anticoagulants (DOACs) are recommended for stroke prevention in Atrial Fibrillation (AF) patients. We aimed to describe the prevalence of inappropriate DOACs dose prescription in the START2-AF Registry, outcomes according to the appropriateness of the dosage, and factors associated with inappropriate dose prescription.
Methods: Patients' demographics and clinical data were prospectively collected as electronic file in anonymous form on the web-site of the START2-Registry; DOACs dosage was defined appropriate when prescribed according to the European Heart Rhythm Association Guideline.
Results: We included 5943 AF patients on DOACs, 2572 (46.3%) females. The standard dose (SD) was prescribed to 56.9% of patients and the low dose (LD) to 43.1% of patients; 38.9% of all AF patients received an inappropriate LD DOAC and 0.3% received inappropriate SD. Patients treated with LD DOAC had a significantly higher rate of all bleedings (RR 1.5; 95% CI 1.2-2.0), major bleedings (RR 1.8; 95% CI 1.3-1.7), and mortality (RR 2.8; 95% CI 1.9-4.1) with respect to patients treated with SD DOAC. Instead, no difference was found among patients treated with appropriate and inappropriate LD regarding bleeding, thrombotic and mortality rates. Age, body weight <60 Kg and renal failure were significantly associated with inappropriate LD DOAC prescription.
Conclusions: Inappropriate LD DOACs in AF patients is not associated with a reduction of bleeding risk, nor with an increased thrombotic risk. Instead, it is associated with higher mortality rate, suggesting that in clinical practice underdosing is preferred for patients at particular high risk for adverse events.

CO024

ASSOCIATIONS OF STRUCTURAL CARDIAC ALTERATIONS WITH SVD NEURORADIOLOGICAL MARKERS IN ELDERLY PATIENTS ON ORAL ANTICOAGULANTS FOR ATRIAL FIBRILLATION: THE STRAT-AF 2 STUDY

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Background and Aims: Neurological complications of Atrial Fibrillation (AF) extend beyond cardioembolic stroke. Neuroradiological assessment of AF patients has revealed a higher risk of cerebral Small Vessel Disease (cSVD), a potential pathological substrate of neurological manifestations. Considering the important role of cardiac dysfunction in the development and maintenance of AF, there is a growing interest in testing the association of cardiac abnormalities with neuroimaging cSVD markers. In the present study we evaluated the association of echocardiographic and cardiac MRI parameters with cSVD markers in a cohort of elderly AF patients on anticoagulant therapy.
Methods: The Strat-AF 2 study (Stratification of cerebral bleeding risk in AF) is an observational single-center hospital-based study that enrolled elderly patients with AF and ongoing anticoagulant therapy at the Centre for Thrombosis of Careggi. All participants underwent a clinical visit and a neuroradiological exam (either brain MRI or head CT), resulting in two different cohorts (MRI and CT cohort). SVD markers were assessed in the total cohort and separately in the MRI and CT cohorts. MRI patients also underwent cardiac MRI.
Results: Of 182 patients enrolled (mean age: 78.6±6.7 years, male sex: 58%, 56% MRI cohort, 44% CT cohort), almost half (47%) presented moderate-to-severe White Matter Hyperintensities (WMHs), 38% had at least one lacune, and 58% had moderate-to-severe cortical atrophy, with a total of 80% having at least one cerebral microangiopathic marker (mean SVD total score=1.6±1.1). In univariate association analyses, higher left atrial volume (LAV) was associated with the prevalence of lacunes (99.1±36.2 *vs.* 85.8±37.0 mL/m2, p=0.021). In patients with moderate-to-severe cortical atrophy we observed higher left and right atrial dimensions (LAV, 97.6±35.3 *vs.* 81.3±38.0 mL/m2, p=0.004; right atrial volume, RAV, 66.1±36.9 *vs.* 55.4±29.7 mL/m2, p=0.047), as well as a higher prevalence of left ventricular hypertrophy (LVH, 51% *vs.* 36%, p=0.043). None of the echocardiographic parameters was associated with WMHs. Correlation analyses, conducted separately in the two cohorts, showed: in the MRI cohort, positive correlations of WMHs with RAVi (r=0.207, p=0.044), microbleeds (MBs) with LAD (r=0.269, p=0.008), basal ganglia-enlarged perivascular spaces (EPVS) with RAVi (r=0.224, p=0.033), SVD total score with LAV (r=0.222, p=0.40), LAVi (r=0.206, p=0.040) and RAVi (r=0.257, p=0.012); in CT cohort, only the SVD total score presented a significant positive correlation with LAD (r=0.231, p=0.042). Cardiac MRI imaging confirmed the association between atrophy and LAVi (122.5±53.9 *vs.* 85.9±26.6 mL/m2, p=0.025) and between MBs and indexed LV mass (73.6±26.6 *vs.* 56.3±20.5 g/m2, p=0.028).
Conclusions: In our cohort, microangiopathic markers were associated with echocardiographic alterations affecting the left and right atria and the left ventricle, suggesting a determining role of arrhythmia-related cardiac substrate in developing the total burden of SVD.

CO025

IMMUNE CELL ANALYSIS AND PLASMA CYTOKINE PROFILE IN FVIII-TREATED AND EMICIZUMAB-TREATED PEDIATRIC HEMOPHILIA A PATIENTS

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Background and Aims: Hemophilia A (HA) is a X-linked disorder caused by reduced or absent activity of coagulation factor VIII (FVIII) due to either mutation or deletion in the FVIII gene. Nowadays, severe pediatric HA patients are treated with FVIII as prophylaxis, with the purpose of keeping its plasma levels above 3% to avoid spontaneous bleedings, increasing the patient's quality of life. The main complication of this therapy is inhibitor formation which are solved by using bypassing agents (or non-replacement therapy) and, more recently, the bispecific antibody Emicizumab. Over the past few years, the shift toward Emicizumab has shown encouraging results in terms of efficacy and safety in clinical trials with adult patients. Conversely, due to restricted reported experience, administration of Emicizumab in neonates, children, and previously untreated patients (PUPs) is limited and still under investigation. The aim of this project is to study the profiles of circulating immune cell population and of circulating plasma cytokines in pediatric HA patients treated only with FVIII, shifted to Emicizumab or patients that never had FVIII infusion but only Emicizumab treatment, comparing them to our control groups, Hemophilia B (HB) patients and Healthy subjects.
Methods: This study analyses patients affected by severe/moderate HA (mean age 10,6 years), HB (mean age 9,3 years), and healthy subjects (mean age 27,3 years). Blood samples were collected in EDTA tubes and processed within 24 hours. Percentages and numbers of blood-derived immune populations were evaluated by flow cytometry. Plasma samples were analyzed using a Multiplex approach, allowing the quantification of 48 different cytokines in each sample. In all analysis, the HA group was further stratified by undergoing treatment, presence of inhibitors, and age (more or less than 10 years).
Results: Among all the myeloid or lymphoid cell populations analysed, FVIII-treated patients have more circulating CD11c+ cells compared to the Emicizumab ones, both in percentage (p=0,0002) and number (p=<0,0001). This data is directly proportional to patients' age (p=0,01). However, when evaluating HLA-DR expression on CD11c+ cells in both groups, Emicizumab-treated patients showed a higher expression compared to FVIII-treated ones in both percentage and median fluorescence intensity (MFI) (p<0,0001). Along with it, HLA-DR expression on CD14+ cells was higher in HA patients compared to healthy subjects for both percentage (p=0,0048) and MFI (p=0,0029). Mutually, cytokines associated with CD14+ cells activity, such as IL12p40, CCL22, IL18, CCL4 and TNFα, were higher in HA plasmas than in healthy ones. Significant differences in inhibitor positive or Emicizumab-only patients were not observed when compared to the other HA patients.
Conclusions: Altogether, these results suggest a difference in the myeloid compartment of HA patients compared to the healthy and, possibly, a different interaction with adaptive immune system between Emicizumab-treated patients and FVIII-treated ones. Most importantly, the plasma cytokine profile shows a higher recall or activation of the monocytes and macrophages, whose role has to be clarified. Eventually, this initial work helps to get additional information related to pediatric hemophilia A patients providing increasing knowledge to maximize the therapeutic effect and reduce or avoid treatment's adverse side effects.

CO026

LONGITUDINAL THROMBO-INFLAMMATORY PROFILING OF INDIVIDUALS UNDERGOING GENDER-AFFIRMING HORMONE THERAPY – HYPERGENDER STUDY

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Background and Aims: Transgender individuals appear to carry an increased risk of venous and arterial thrombosis related to the hypercoagulability driven by gender-affirming hormone therapy (GAHT). The mechanisms underpinning these harmful relationships are not known. The aim of this longitudinal cohort study is to investigate the effects of GAHT on coagulation, metabolism and erythropoiesis, exploring the mechanisms underlying the hypercoagulability in transgender population.
Methods: Adult transgender subjects who initiated GAHT at the University Hospital of Padova between December 2022 and November 2023 underwent plasma venous samples at baseline (before the start of GAHT) and at 3 and 6 months after starting GAHT to assess complete blood count, levels of sex hormones, presence of hereditary thrombophilia, procoagulant factor VIII and fibrinogen, protein C, protein S, antithrombin, thromboelastometry, whole blood aggregometry, iron metabolism, and erythropoietin. Full clinical examination was performed at baseline and during the follow-up. Non-parametric Wilcoxon test for paired data was used to evaluate longitudinal changes in coagulation, metabolism and iron pathway parameters after 6 months of GAHT.

Table 1.

Longitudinal trend of blood count, sex hormones, metabolic, coagulation and iron metabolism parameters in transgender subjects undergoing gender-affirming hormone therapy.

Assigned Male at Birth -AMAB				
Parameter	Baseline	3 months	6 months	p for trend
Blood count				
Hb - g/dL	15.3 [15-16]	13.3 [12.6-13.9]	14.7 [14.2-15.2]	ns
HCT - %	45.9 [44.7-48.3]	40.4 [37.4-42.2]	42.6 [40.9-44.6]	ns
PLTs – x 10^3/L	244 [203-276]	291 [210-349]	277 [206-369]	**0.0033**
Sex steroids				
Testosterone – ng/mL	5.3 [4.2-6.5]	0.2 [0.1-0.3]	0.3 [0.2-1.2]	**0.006**
Estradiol (E2) – ng/L	33.6 [26-35]	40.7 [34-83]	167 [51-289]	ns
SHBG – nmol/L	40.3 [40-40.7]	39.2 [38.5-40]	-	ns
LH – U/L	5.3 [3.5-7.3]	0.2 [0.1-0.3]	0.2 [0.1-2.9]	**0.0002**
FSH – U/L	2.4 [1.9-3.9]	0.4 [0.35-0.6]	0.5 [0.4-1.5]	ns
Metabolic parameters				
BMI – Kg/m^2	24.9 [20.2-26.9]	22.6 [19.8-26.9]	22.4 [20.3-26.9]	ns
Total cholesterol- mg/dL	139 [128-186]	-	128 [111-143]	ns
HDL – mg/dL	49 [46-51]		48 [46-56]	ns
Triglycerides – mg/dL	97 [68-99]		65 [41-86]	ns
C-reactive protein – mg/dL	0.6 [0.43-0.7]	-	0.65 [0.35-0.84]	ns
Procoagulant factors				
Factor VIII activity - %	113 [97-133]	115 [98-131]	108 [92-127]	ns
Fibrinogen activity – mg/dL	323 [290-390]	318 [252-353]	307 [282-340]	ns
Anticoagulant factors				
Protein C activity - %	100 [85-106]	93 [87-101]	101 [94-108]	ns
Protein S activity - %	109 [102-123]	123 [114-125]	128 [122-134]	**0.007**
Protein S free antigen - %	102 [96-115]	107 [99-115]	119 [101-121]	ns
Antithrombin - %	98 [89-102]	101 [88-119]	97 [94-109]	ns
Thromboelastometry				
CFT-INTEM - sec	89 [71-99]	177 [147-206]	59 [57-76]	**0.003**
MCF-INTEM – mm	61 [57-66]	62 [61-64]	63 [62-65]	ns
MCF-EXTEM – mm	65 [61-67]	63 [62-67]	66 [65-67]	ns
MCF-FIBTEM - mm	16 [12-16.5]	15 [13.5-23]	16 [15.7-20.5]	ns
Whole blood aggregometry				
TRAP – AUC	99 [94-117]	108 [87-134]	142 [133-145]	**0.05**
ADP – AUC	81 [64-103]	79 [53-95]	80 [72-92]	ns
ASPI - AUC	72 [57-86]	73 [62-81]	89 [68-91]	ns
Iron metabolism				
Iron – umol/L	9.5 [5.9-16.4]	19.5 [11.5-20]	15.4 [11.6-19]	ns
Ferritin – ng/mL	131 [77-168]	96 [91-187]	108 [105-176]	ns
Transferrin – g/L	2.7 [2.2-3.3]	2.4 [2.2-2.6]	2.6 [2.3-2.9]	ns
Assigned Feminine at Birth -AFAB				
Parameter	Baseline	3 months	6 months	p for trend
Blood count				
Hb - g/dL	13.3 [12.8-13.5]	14 [13.5-14.5]	14.6 [14.4-14.9]	**0.0006**
HCT - %	40.5 [39.9-40.9]	43 [42-44.2]	44.8 [43-46.4]	**<0.0001**
PLTs – x 10^3/L	255 [233-299]	277 [227-306]	253 [243-274]	ns
Sex steroids				
Testosterone – ng/mL	0.3 [0.24-0.39]	3 [2.5-5.2]	4.8 [2.3-14.9]	**<0.0001**
Estradiol (E2) – ng/L	69 [43-111]	40 [32-75]	42 [29-67]	ns
SHBG – nmol/L	80.7 [53-99]	47.9 [33.4-54.3]	37.2 [27-41]	**0.02**
LH – U/L	5.5 [4.1-9.3]	8.6 [4.6-13.8]	6.2 [2.6-14.9]	ns
FSH – U/L	5.2 [3.8-6]	4.8 [3.6-7.2]	5 [2.5-7.2]	ns
Metabolic parameters				
BMI – Kg/m^2	24.4 [19.7-24.9]	23.3 [19.8-25]	22.5 [19.8-27]	ns
Total cholesterol- mg/dL	120 [128-185]	-	130 [127-190]	ns
HDL – mg/dL	58 [53-62]		50 [45-54]	ns
Triglycerides – mg/dL	63 [57-82]		72 [58-86]	ns
C-reactive protein – mg/dL	0.6 [0.5-0.6]	0.2 [0.09-3.4]	0.04 [0.02-3.2]	ns
Procoagulant factors				
Factor VIII activity - %	133 [97-149]	134 [120-159]	130 [94-139]	ns
Fibrinogen activity – mg/dL	357 [314-424]	332 [289-371]	339 [290-359]	ns
Anticoagulant factors				
Protein C activity - %	109 [89-118]	102 [89-129]	110 [91-128]	ns
Protein S activity - %	107 [91-114]	131 [104-146]	128 [116-134]	**0.002**
Protein S free antigen - %	95 [91-108]	113 [106-118]	106 [103-119]	ns
Antithrombin - %	98 [96-109]	99 [93-108]	98 [94-102]	ns
Thromboelastometry				
CFT-INTEM - sec	65 [56-70]	70 [65-82]	87 [67-107]	ns
CFT-EXTEM - sec	70 [61-86]	77 [71-85]	93 [71-95]	**0.01**
MCF-INTEM – mm	65 [61-69]	62 [58-67]	60 [56-66]	**0.02**
MCF-EXTEM – mm	69 [64-72]	65 [63-69]	64 [61-68]	**0.04**
MCF-FIBTEM - mm	20 [14-24]	15 [14-17]	15 [11-17]	**0.0007**
Whole blood aggregometry				
TRAP – AUC	105 [81-123]	112 [105-130]	109 [97-136]	ns
ADP – AUC	71 [49-87]	65 [59-68]	72 [55-89]	ns
ASPI - AUC	73 [49-92]	60 [52-69]	74 [59-80]	ns
Iron metabolism				
Iron – umol/L	7.9 [7.4-12]	5.2 [4.5-6.7]	20.5 [10.5-36]	ns
Ferritin – ng/mL	23 [15-56]	12 [6-15.5]	19 [13-23.2]	**0.02**
Transferrin saturation - %	9 [8.9-12.1]	6 [5.2-7.6]	1.9 [1.4-5.3]	**0.04**

Data are expressed as median and [interquartile range]

Hb: hemoglobin; HCT: hematocrit; PLT: platelets; BMI: body mass index; HDL: high density lipoprotein; SHBG: sex hormone binding globulin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; CFT: clotting formation time; MCF: maximum clot firmness; TRAP: Thrombin Receptor-Activating Protein; AUC: area under the curve.

Results: We recruited 81 transgender subjects (31 Assigned Male At Birth [AMAB] and 50 Assigned Feminine At Birth [AFAB]) who initiated GAHT. As for AMAB, mean age 29.5±12.3 years; mean BMI 24.9±6.1 Kg/m2; 12% had family history of thrombosis; 32% active smokers; 16% had cardiovascular risk factors; 13% had anxiety/depression; 10% had hereditary thrombophilia (1 factor V Leiden and 2 prothrombin mutation); all AMAB have undertaken transdermal estrogen therapy without association with anti-androgen compounds. As for AFAB, mean age 23.5±5.2 years; mean BMI 24.4±4.5 Kg/m2; 18% had family history of thrombosis; 30% active smokers; 12% had cardiovascular risk factors; 4% had previous cancer; 22% had anxiety/depression; 8% had hereditary thrombophilia (4 factor V Leiden); all AFAB have undertaken testosterone therapy, of whom 82% transdermal, 16% intramuscular and 2% oral. Regarding the longitudinal monitoring, for AMAB, a significant increase in platelet count, protein S activity and TRAP- Thrombin Receptor-Activating Protein aggregometry was detected 3 and 6 months after starting GAHT. A significant shortening of CFT-INTEM (clotting formation time) was observed at 6 months. As for AFAB, a significant increase of hemoglobin, hematocrit and iron with a decrease of ferritin and transferrin saturation was detected. Interestingly, a significant prolongation of CFT-EXTEM with decrease of MCF in INTEM, EXTEM and FIBTEM was observed at thromboelastometry (Table 1). No significant correlations were detected between sex hormones and coagulative parameters. No thrombotic event was recorded during the follow-up.

Conclusions: This longitudinal analysis reveals early changes in thrombo-inflammatory parameters in subjects undergoing 6-month GAHT. Namely, AMAB appear to have increase platelet count and thrombin-driven aggregability, while the main changes for AFAB pertain to iron metabolism and erythrocytosis. Finally, we observed that 8-9% of subjects undergoing GAHT carry hereditary thrombophilia. Wider cohorts with longer follow-up are needed to better evaluate GAHT-driven hypercoagulable changes.

CO027

PROMINENT ROLE OF PM10 AND PLATELETCRIT IN THE LINK BETWEEN AIR POLLUTION AND INCIDENT PARKINSON'S DISEASE: FINDINGS FROM A LONGITUDINAL ITALIAN POPULATION COHORT

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Background and Aims: Air pollution has been associated with Parkinson's Disease (PD) risk, although this relationship and the underlying mechanisms remain unclear. The aim of the present study was to clarify the influence of air pollution on incident PD risk and potential mediation pathways at the level of circulating biomarkers, including platelet parameters.
Methods: We estimated yearly levels of exposure to ten different pollutants (period 2006-2018) in the Moli-sani study, an Italian population cohort (N=24,325; ≥35 years; 51.9% women, baseline recruitment 2005-2010). We derived principal components (PCs) from pollutants levels and tested their associations with incident PD cases - identified by record linkage to hospital discharge and drug prescription registries - through multivariable Cox Proportional Hazard regressions adjusted for age, sex, education, and several professional and lifestyle exposures. Moreover, we tested whether specific pathways tagged by circulating markers may explain part of this association.
Results: We identified three PCs explaining ≥5% of pollution exposure variance: PC1 (38.2%, tagging PM10), PC2 (19.5%, O3/CO/SO2), PC3 (8.5%, NOx/BTX hydrocarbons). Over 23,841 participants (213 incident PD cases, median(IQR) follow-up 11.2(2.0) years), we observed a statistically significant association of PC1 with an increased PD risk (1.05[1.03-1.07]; p=5×10-6), independent on other covariates. The association was confirmed testing average PM10 levels during follow-up (19[13-24]% increase of PD risk per 1 µg/m3 of PM10). Among the pathways tested, plateletcrit (***i.e.*** the volume occupied by platelets in the blood) explained a notable proportion of this association (34.0 (4.6-52.7)%), being positively associated with both PM10 and PD.
Conclusions: These findings suggest PM10 as a target to lower PD risk at the population level and a potential role of platelets – peculiarly plateletcrit, a marker of platelet activity and inflammation – in the underlying mechanisms, in line with previous studies implicating platelets in PD etiology at the epidemiological, genetic and functional level.

CO028

LOW GRADE INFLAMMATION IN LONG-COVID SYNDROME SUSTAINS A DISTINCTIVE PLATELET ACTIVATION PHENOTYPE ASSOCIATED WITH PULMONARY IMPAIRMENT

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Background and Aims: Long-COVID syndrome is characterized by symptoms persisting after acute infection remission. We previously documented that, in acute COVID-19 patients, platelets show a prothrombotic phenotype characterized by increased P-selectin and Tissue Factor (TF) expression and platelet-leukocyte aggregate formation. Whether this phenotype can sustain the residual pulmonary impairment observed in Long-COVID patients has yet to be established. The aim of the present study was therefore to characterize platelet activation persistence, the underlying mechanisms, and the possible relationship with pulmonary function 6-month after acute COVID-19 remission.
Methods: Among 204 enrolled subjects with a 6-month follow-up post-SARS-CoV-2 infection, 34 patients reporting symptoms suggestive of Long-COVID were compared with 34 COVID-Recovered asymptomatic patients and 34 healthy subjects (HS). Platelet activation (P-selectin, TF, platelet-monocyte and platelet-granulocyte aggregates [PMA and PGA]) profile was measured by flow-cytometry; *ex vivo* thrombus formation was analysed by perfusion of collagen-coated microfluidic chambers with patients' blood. Plasma levels of C-reactive protein (CRP), Interleukin-6 (IL-6), and lung diffusion (DLNO) and pulmonary CT scan were evaluated. The pharmacological modulation of platelet activation was assessed in *ex vivo* mixing experiments.
Results: A 7-fold higher levels of CRP, but not IL-6, were measured in Long-COVID compared to COVID-Recovered patients. The percentage of P-selectinpos platelets was significantly greater in symptomatic than in the asymptomatic subjects (2.5-fold, p<0.0001) and HS (7-fold, p<0.0001). As a result, the percentage of PGA and PMA was greater than in Long-COVID compared to COVID-Recovered (1.5-fold, p=0.0065; 1.3-fold, p=0.0273, respectively) and HS (1.5-fold, p=0.0015; 2-fold, p<0.0001, respectively). PGA and PMA were associated with residual lung damage at CT (p=0.0043 and p=0.0056, respectively) and DLNO (p=0.0360 and p=0.0487, respectively). *Ex vivo*, blood from Long-COVID patients formed, on collagen-coated surfaces, a number of microthrombi significantly greater than blood from HS. Plasma from Long-COVID patients mixed with HS blood induced P-selectin expression and platelet-leukocyte aggregate formation through a CRP- and IL-6-dependent mechanism, features prevented by Fcγ-receptor inhibitor, tocilizumab, aspirin, and P2Y12 antagonist.
Conclusions: Long-COVID patients present increased CRP levels together with a high percentage of platelet-leukocyte aggregates that significantly cor-

relate with residual parenchymal damage. In *ex vivo* experiments, low-grade inflammation in Long-COVID plasma mediates platelet activation which was blunted by antiplatelet and antiinflammatory drugs. These results may have relevant clinical implications as they suggest the biomarkers to be measured in order 1) to fine-tune the clinical status and, based on this, 2) to tailor the drug therapy. To date, indeed, no pharmacological treatment has proven to be clearly beneficial in the management of Long-COVID syndrome.

CO029

LOW-GRADE INFLAMMATION AND CANCER RISK: PROSPECTIVE RESULTS FROM THE MOLI-SANI STUDY

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Background and Aims: While the importance of inflammation in cardiovascular health is well-established, it is equally intriguing to explore its role in cancer, highlighting the interconnectedness of these seemingly distinct pathological processes. Chronic inflammation and cancer may influence each other: chronic inflammation may underlie and promote cancer development, and solid tumors may induce an inflammatory microenvironment and a systemic host immune response. In recent years, few population studies suggested that a state of low-grade inflammation, usually measured by a single biomarker, appears to be related to a higher risk of cancer development. However, the evidence of a potential link between silent low-grade inflammation and cancer remains limited. The Moli-sani study proposed and tested a composite score to assess low-grade inflammation, the INFLA-score. The present study aimed to evaluate the association of this low-grade inflammation score with whole cancer mortality, first hospitalization for any malignant neoplasm and fatal and not fatal colorectal cancer (CRC).

Methods: A prospective investigation was performed on 18,933 subjects (51.9% women; mean age±SD: 55.8±12.0 years), free from cancer and an acute inflammatory status at baseline (2005-2010) enrolled by the Moli-sani study. Low-grade inflammation was evaluated by a composite score of four biomarkers of inflammation (C-reactive protein, leukocyte and platelet count, granulocyte/lymphocyte ratio); the INFLA-score, ranged between -16 and 16, an increase in the score represented an increase in low-grade inflammation intensity. Hazard ratios (HR) and 95% confidence interval (CI) for cancer mortality, cancer hospitalization and fatal and not fatal CRC according to quintiles of INFLA-score were calculated using Cox proportional hazard models with time-on-study on the time scale.

Results: Over a median follow-up of 13.1 years (interquartile ranges: 12.1-14.1), a total of 612 any cancer deaths, 1,854 first hospitalizations for malignat neoplasm and 287 fatal and not fatal CRC cases were ascertained. In multivariable-adjusted analyses, compared with subjects in the lowest quintiles (Q1-Q4) of INFLA-score, those in the highest had an increased hazard in cancer hospitalization and in fatal and not fatal CRC (HR: 1.20, 95% CI: 1.08-1.34 and HR: 1.68, 95% CI: 1.30-2.18, respectively; Figure 1). These findings were confirmed by excluding cases that occurred during the first 12 months of follow-up, reducing the likelihood that these subjects already had cancer at the baseline visit. Similar, but less robust results were found for cancer mortality (HR: 1.19, 95% CI: 0.99-1.43). However, when the analyses were stratified by age classes (35-65 years, ≥65 years), a higher cancer mortality rate (32%) was observed in the elderly with elevated level of low-grade inflammation (HR: 1.32, 95% CI: 1.03-1.69; Figure 1).

Conclusions: A higher level of low-grade inflammation, measured by a composite score, is an independent risk factor for cancer hospitalization and colorectal cancer in a general adult population with no acute inflammation at baseline. Whereas, the association with cancer mortality was more pronounced among the elderly. A good clinical management of the low-grade inflammation condition could lead to a reduction in the burden of cancer and, consequently, a decrease in the national healthcare system needs.

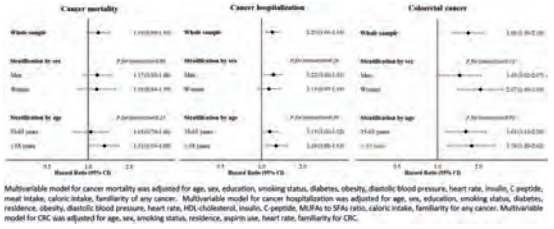

Figure 1.

CO030

BIOMARKERS OF INFLAMMATORY AND ENDOTHELIAL ACTIVATION STATE MAY PREDICT AN INCREASED RISK OF CANCER OCCURRENCE IN HEALTHY SUBJECTS: RESULTS FROM THE HYPERCAN STUDY

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Background and Aims: The relationship between inflammation, coagulation, and tumor progression has been known for many years. Additionally, there is substantial evidence indicating that chronic inflammation associated with endothelial perturbance can also increase the likelihood of developing cancer. The objective of this exploratory study is to determine if the presence of an inflammatory state can predict cancer diagnosis in a group of healthy individuals enrolled in the HYPERCAN study (Falanga *et al.*, Thromb Res 2016).
Methods: From 2012 to 2022, 10,294 healthy blood donors from Bergamo province were enrolled in the HYPERCAN study and followed up for cancer occurrence. Blood samples were collected at enrolment (T0) and after 6-18 months (T1), together with clinical, hematological data and a lifestyle questionnaire. For this explorative study, we analyzed a sub-cohort of 102 subjects. Plasma level of C reactive protein (CRP, apDia BV ELISA kit) was used as an inflammatory biomarker. Plasma levels of thrombomodulin (Abcam ELISA kit) and Von Willebrand factor antigen (vWF-Ag, ACL TOP 500, Werfen) served as endothelial activation biomarkers. All statistical analyses were performed using R (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria).
Results: The HYPERCAN sub-cohort included 102 subjects, 69 males and 33 females, with a median age of 50 years (range 35-64). Specifically, 67 of them were cancer cases (47M/20F) with a median age of 52 years (range 35-64), while 35 were controls (22M/13F) with a median age of 46 years (range 35-63). The most diagnosed tumor sites were the prostate in males (20%) and the breast in females (12%). At time T0, cancer cases showed significantly higher levels of CRP (0.80±1.36 ug/mL *vs* 0.08±0.17 ug/mL, p<0.001) and thrombomodulin (4.26±1.56 ng/mL *vs* 3.36±1.46 ng/mL, p=0.006) compared to the control group. This trend continued at time T1, where plasma levels of CRP (0.82±1.57 *vs* 0.12±0.31 ng/mL; p<0.001) and thrombomodulin (4.09±1.77 *vs* 3.14±1.34 ng/ml; p=0.003) remained significantly higher in cancer cases compared to controls. There were no statistically significant differences in vWF-Ag levels between the two groups. Additionally, linear regression analysis established an association between CRP and thrombomodulin levels (B=0.180, p=0.013). Linear multivariate analysis corrected for age and gender showed that having at enrolment high levels of CRP and thrombomodulin and being older were factors significantly associated with cancer occurrence (p<0.05).
Conclusions: Our initial findings show that high levels of CRP and thrombomodulin are significantly linked to a cancer diagnosis, and this association is confirmed at two different time points. Therefore, an inflammatory status that may lead to endothelial activation could be valuable in identifying individuals at a higher risk of developing cancer.

CO031

EXTRACOAGULATIVE ROLE OF FVIII ON MURINE BONE CELL DIFFERENTIATION AND FUNCTION

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Background and Aims: Several clinical and pre-clinical studies highlight the complex interplay between hemophilia A (HA) and skeletal health. HA patients exhibit low bone mineral density (BMD) and a heightened fracture risk and HA murine models mirror these clinical observations, even under conditions of similar physical activity and of hemarthroses absence. To date, the precise impact of FVIII deficiency on skeletal health across different life stages remains unclear. Decreased skeletal health may be caused by altered signalling between cells that are responsible for bone remodelling: osteoblasts, for building, and osteoclasts, for resorption. Therefore, the purpose of this study is to unveil whether and how FVIII affects 1. *in vivo* the BMD over time in absence of possible confounding factors and 2. *in vitro* maturation and activity of osteoblasts and osteoclasts.
Methods: Trabecular and cortical bone parameters were measured respectively on tibias and femurs obtained from HA and wild-type (wt) age-matched C57BL/6 mice at different time points: week 3, 8, 24, and 52. HA and wt osteoblast precursors were isolated from the bones of 3-week-old mice by collagenase treatment while myelomonocytic progenitors were flushed out from the bone marrow (BM) at week 8. Osteoblast differentiation was induced with ascorbic acid and β-glycerophosphate in presence or absence of FVIII; instead, osteoclastogenesis was promoted by M-CSF and RANKL±FVIII supply. Differentiation and mineralization of osteoblasts were assessed using the Alkaline Phosphatase and Alizarin-Red-S assays, while osteoclastogenesis was evaluated by the TRAP staining. Confirmation of osteoblast maturation was evaluated by qPCR analysis of several osteoblast-associated genes.
Results: Overall, HA compared to wt mice showed a reduced trabecular bone volume, coupled with an increase in trabecular space. Interestingly, no significant differences were detected in the cortical parameters. *In vitro* differentiation and mineralization of osteoblasts were compromised in HA compared to wt samples. In accordance, the gene expression of the main regulators of osteoblastic differentiation, *BMP-2* and *RUNX2*, and of bone matrix deposition, *ALPL* and *COL1A1*, was downregulated in HA *versus* wt osteoblasts. Interestingly, FVIII supply restored *in vitro* HA osteoblasts differentiation and mineralization. Instead, HA-derived BM progenitors displayed a greater *in vitro* osteoclastogenesis which was not affected by FVIII supplementation.
Conclusions: The *in vivo* longitudinal assessment of bone parameters confirmed the previous pre-clinical and clinical findings on the decreased loss of BMD in hemophilic patients, highlighting the impairment of the trabecular bone structure. In accordance, the results obtained in

the *in vitro* differentiation studies showed an impaired balance of osteoblast and osteoclast maturation in FVIII absence, in favor of bone resorption.

CO032

RESCUE OF A PANEL OF SPLICING MUTATIONS CAUSING HEMOPHILIA A BY ENGINEERED U1-SNRNAS

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Background and Aims: Hemophilia A (HA) is an X-linked recessive hemorrhagic disorder caused by coagulation factor VIII (FVIII) deficiency. Point mutations altering the splicing process and often leading to complete exon skipping are relatively common among all HA-causing mutations, especially in severe forms. These kinds of mutations can be potentially rescued by RNA therapeutics based on engineered variants of the key spliceosomal component U1snRNA, as already shown in several human disease models. Here, we dissected the molecular mechanisms of nine F8 splicing variants identified in HA patients and located at the 5' splice sites (5'ss) of exon 6 (c.787+2T>C; c.787+3A>G; c.787+3A>T; c.787+5G>A; c.787+6T>C), exon 11 (c.1752+5G>T; c.1752+5G>C; c.1752+5G>A) and exon 22 (c.6429+5G>T) and explored engineered U1snRNAs to restore the correct pre-mRNA processing.
Methods: Creation of expression vectors for i) the splicing competent minigenes carrying the F8 wild-type or variants-containing exons 6, 11, or 22 along with the corresponding surrounding introns as well as ii) the engineered U1snRNAs designed to bind to the mutated 5'ss (compensatory U1snRNA) or to less-conserved downstream intronic sequences (Exon Specific U1snRNA, ExSpeU1snRNA). HEK293T cells were transiently transfected with these expression vectors, and RT-PCR using plasmid-specific primers was used to evaluate the splicing patterns.
Results: The bioinformatic analysis with SpliceRover predicted that F8 exons 6, 11, and 22 are well-defined exons and that the mutations would weaken the canonical 5'ss rather than activating cryptic 5'splice sites.
The *in vitro* splicing pattern analysis revealed that these mutations lead to exon skipping with low levels (5-30% based on mutation position within the 5'ss) of correctly spliced transcripts. The reduced levels of correctly spliced transcripts are consistent with the associated coagulation phenotype and FVIII antigen levels, whenever available. Notably, co-transfection of the U1snRNA variants significantly improved definition of the defective F8 exon 6, exon 11, and exon 22, and their inclusion up to 95%. Moreover, different mutations occurring at the same 5'ss can be rescued by a single engineered U1snRNA.
Conclusions: We provide experimental evidence on the causative nature of the mutations that affect correct exon definition and trigger aberrant splicing, and the residual proportion of correct transcripts is consistent with the patients' coagulation FVIII levels. Importantly, we demonstrated that engineered U1snRNA variants can efficiently restore exon 6, exon 11 and exon 22 definition and one ExSpeU1snRNA can rescue multiple splicing mutations occurring at the same 5'ss. These RNA therapeutics are currently under investigation through lentiviral-mediated delivery in Blood Outgrowth Endothelial Cells (BOECs) isolated from HA patients.

CO033

CLINICAL AND PATIENT-CENTERED OUTCOMES AMONG ITALIAN PEOPLE WITH SEVERE HAEMOPHILIA A RECEIVING PROPHYLAXIS: REAL-WORLD FINDINGS FROM THE 'COST OF HAEMOPHILIA: A SOCIO-ECONOMIC SURVEY' (CHESS) DATA BASE

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Background and Aims: Limited evidence is available describing how burden of illness measures change in the context of an evolving treatment paradigm for people with severe haemophilia A (PwSHA).
This analysis aimed to evaluate clinical and patient-reported outcomes (PROs) in a sample of Italian PwSHA, alongside current/historical clinical characteristics and treatment approaches.
Methods: Descriptive analysis examined data on non-inhibitor PwSHA receiving emicizumab or FVIII prophylaxis from the CHESS data platform (2019-2022) (a repeated European cross-sectional retrospective, burden-of-illness study conducted in adult PwH) within two non-mutually-exclusive groups: one comprising individuals with a physician questionnaire (Full-cohort) and another with complete patient forms (PRO-cohort).
Results: Of 238 PwSHA enrolled in Italy with ≥6months on current treatment, 121 (51%) were on emicizumab and 117 (49%) on FVIII prophylaxis, with a mean age of 35.4 and 38.3. Of these, 125 (52%) completed a patient-form [78 (62%) on emicizumab and 47 (38%) on FVIII] (Table 1). Mean-all-bleed annualized bleeding rate

(ABR) was 2.0 and 3.8, and number of problem joints 0.5 and 1.2 for the emicizumab and FVIII cohorts, respectively. Moderate/severe chronic pain was reported in 12.4% and 38.4% of the emicizumab and FVIII cohorts, respectively. Among emicizumab patients with pre-switch bleeding data (n=108), a reduction in ABR was observed *vs.* previous treatment regimen (1.8 *vs* 2.8), with 78.7% switching from FVIII prophylaxis. Comparing the emicizumab and FVIII cohorts, PRO analysis showed higher EQ-5D scores (0.76 *vs.* 0.59) and lower caregiver requirement (25.6% *vs* 44.7%), work productivity loss (25.7% *vs.* 34.2%) and activity impairment (23.3% *vs.* 30.0%) and anxiety/depression, measured with GAD-7 (4.4 *vs.* 9.0) and PHQ-8 (6.0 *vs.* 7.8) in emicizumab cohort.
Conclusions: These findings suggest that PwSHA in this cohort experiencing sub-optimal bleed control switching to emicizumab, generally experience reductions in ABR. The emicizumab cohort reported favorable joint and pain outcomes and EQ5D, mental health and productivity scores.

Table 1.

Patient characteristics, clinical and treatment outcomes (Full cohort)

	Emicizumab	Prophylactic FVIII
Full cohort	**N=121**	**N=117**
Age, *Mean (SD)*	35.4 (16.3)	38.3 (13.6)
BMI, *Mean (SD)*	25.2 (2.5)	24.5 (2.5)
Current FVIII treatment class, *N (%)*		
Extended Half-Life	*Not applicable*	26 (22.2%)
Standard Half-Life	*Not applicable*	69 (59.0%)
Plasma-Derived	*Not applicable*	22 (18.8%)
ABR, *Mean (Median, Range)*[a]	2.0 (1.3, 0-14)	3.8 (3.0, 0-25)
Problem joints[b], *Mean (Median, Range)*	0.5 (0.0, 0-4)	1.2 (1.0, 0-4)
Chronic pain level[c], N(%)		
None	39 (32.2%)	18 (15.4%)
Mild	67 (55.4%)	54 (46.2%)
Moderate	13 (10.7%)	35 (29.9%)
Severe	2 (1.7%)	10 (8.5%)
Pre-post emicizumab cohort	**N=108**	
ABR, *Mean (Median, Range)*	1.8 (1.3, 0-14)	*Not applicable*
ABR on previous treatment[d], *Mean (Median, Range)*	2.8 (2.0, 0-20)	*Not applicable*
Previous treatment strategy, *N (%)*		
FVIII Prophylaxis	85 (78.7%)	*Not applicable*
FVIII On-demand	23 (21.3%)	*Not applicable*

Abbreviations: FVIII, Factor VIII; BMI, body mass index; SD, standard deviation; ABR, Annualised Bleed Rate
Notes: [a]ABR was annualized based on the duration of the current treatment strategy (when duration of current treatment was ≥6 months; when treatment duration was ≥12 months, annual bleeding rate was used. [b]Any joint that has been permanently damaged as a result of the patient's bleeding disorder (having chronic joint pain and/or limited ranged of movement due to compromised joint integrity [i.e., chronic synovitis and/or haemophilic arthropathy]), with or without persistent bleeding. [c]Chronic pain was defined as: "None" (no functional deficit, no analgesic use except with acute haemarthrosis); "Mild" (does not interfere with occupation nor with activities of daily living, may require occasional non-narcotic analgesic); "Moderate" (partial or occasional interference with occupation or activities of daily living, use of non-narcotic medications); "Severe" (interferes with occupation or activities of daily living; requires frequent use of non-narcotic and narcotic medications). [d]Information only available for switches from replacement to non-replacement

CO034

SEVEN-YEAR FOLLOW-UP OF VALOCTOCOGENE ROXAPARVOVEC GENE THERAPY FOR HAEMOPHILIA A

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Background and Objectives: Valoctocogene roxaparvovec is an adeno-associated virus vector serotype 5 (AAV5)-mediated gene therapy approved for severe haemophilia A (HA). The aim is to update on seven-year follow-up of valoctocogene roxaparvovec gene therapy for haemophilia A.
Methods: In this open-label, phase 1/2 dose-escalation trial (NCT02576795), males ≥18 years with severe HA (factor VIII [FVIII] ≤1 IU/dL) who were previously receiving exogenous FVIII and had no history of FVIII inhibitors or anti-AAV5 antibodies received an infusion of 6e13 (n=7) or 4e13 (n=6) vg/kg valoctocogene roxaparvovec. Efficacy was assessed by FVIII activity (chromogenic assay), bleeding and exogenous FVIII use; safety was assessed with reported adverse events.
Results: At years 7 and 6, median (interquartile range) FVIII activity was 10.3 (4.8–14.2) and 7.2 (4.5–8.9) IU/dL in the 6e13 (n=5) and 4e13 (n=4) cohorts, respectively. In the last year, estimated FVIII activity changed by −0.001 and −0.07 IU/dL/week for the 6e13 and 4e13 cohorts, respectively. During all follow-up, mean ABRs decreased from BL by 96% and 88% for the 6e13 and 4e13 cohorts at years 7 and 6, respectively. A 6e13 cohort participant resumed prophylaxis after a non–treatment-related grade 4 SAE of spontaneous internal carotid artery bleeding in year 7. Another 6x1013 cohort participant resumed prophylaxis in year 7 following ankle joint bleeds; 6 weeks prior, his FVIII activity was 1.9 IU/dL. A 4e13 cohort participant transiently returned to prophylaxis during year 5. Mean (median) annualized FVIII infusion rate for the 6e13 and 4e13 cohorts were 6.4 (1.6) and 9.3 (5.1) infusions/year over all follow-up, a decline of 95% and 93% from BL, respectively. In the last year, 1 participant in each cohort had a treatment-related AE: grade 1 hepatomegaly (6e13) and grade 1 splenomegaly (4e13).
Conclusions: While 2 participants resumed prophylaxis in year 7, the majority maintained haemostasis. Safety remains in line with previous reports.

CO035

EFFICACY AND SAFETY OF VALOCTOCOGENE ROXAPARVOVEC 4 YEARS AFTER GENE TRANSFER IN GENER8-1

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Background and Objectives: Valoctocogene roxaparvovec (AAV5-hFVIII-SQ), a gene transfer therapy for severe hemophilia A, enables endogenous factor VIII (FVIII) production to prevent bleeding. Evaluate efficacy and safety outcomes 4 years post-valoctocogene roxaparvovec treatment.

Methods: In the open-label, multicenter, phase 3 GENEr8-1 trial (NCT03370913), 134 adult men with severe hemophilia A (FVIII ≤1 IU/dL) without FVIII inhibitors received 6E13 vg/kg valoctocogene roxaparvovec (intention-to-treat [ITT] population). Bleeds and FVIII use were self-reported after regular prophylaxis cessation (scheduled week [W]4). The rollover population, which included 112 HIV-negative participants who enrolled from a non-interventional study, was used for comparisons with baseline FVIII use and bleeding rate. Chromogenic (CSA) and one-stage assay (OSA) FVIII activity was assessed in 132 HIV-negative participants (modified ITT [mITT] population). Safety was assessed in the ITT population.

Results: In the ITT population, 118/134 participants completed W208; 24/134 participants resumed prophylaxis. In the rollover population, mean annualized treated bleeding rate was 0.8 bleeds/y, mean annualized bleeding rate for all bleeds was 1.3 bleeds/y, and mean annualized FVIII infusion rate was 6.1 infusions/y over 4 years. During year 4, 81/110 (73.6%) participants had 0 treated bleeds and 68/110 (61.8%) participants had 0 bleeds regardless of treatment. At W208, mean CSA and OSA FVIII activity was 16.1 and 27.1 IU/dL, respectively, in the mITT population (18.0 and 25.5 IU/dL at W260 for the mITT subgroup dosed ≥5 years prior; Figure 1); 10/130 (7.7%), 68/130 (52.3%), 18/130 (13.8%), and 34/130 (26.2%) participants had CSA FVIII activity ≥40, ≥5 to <40, ≥3 to <5, and <3 IU/dL, respectively. During year 4, the most common adverse event was alanine aminotransferase (ALT) elevation (56/131 participants; ALT >upper limit of normal or ≥1.5x baseline); no participants initiated immunosuppressants for ALT elevation.

Conclusions: Bleed control and FVIII expression were maintained 4 years post-valoctocogene roxaparvovec treatment. No new safety signals emerged.

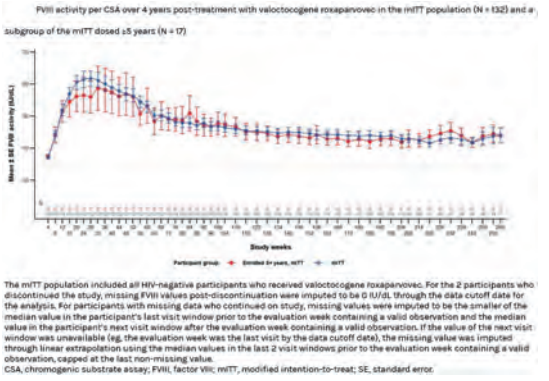

Figure 1.

CO036

HEALTH-RELATED QUALITY-OF-LIFE OUTCOMES 4 YEARS AFTER TREATMENT WITH VALOCTOCOGENE ROXAPARVOVEC

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Background and Objectives: Valoctocogene roxaparvovec, a gene therapy for severe hemophilia A (HA), helps prevent bleeding by providing the body with genetic instructions for making factor VIII (FVIII) protein. We report findings from the GENEr8-1 study 4 years after participants received valoctocogene roxaparvovec. To compare health-related quality-of-life (HRQOL) outcomes before and after treatment with valoctocogene roxaparvovec.

Methods: In GENEr8-1, 134 adult men with severe HA received one infusion of valoctocogene roxaparvovec (6E13 copies of FVIII instructions/kg). To assess their HRQOL, participants completed questionnaires before receiving valoctocogene roxaparvovec and regularly afterwards. The Haemo-QOL-A, a questionnaire designed for HA and B, is being validated for gene therapy for HA. It produces a Total Score reflecting overall HRQOL and domain scores measuring impacts on specific aspects of life, such as Physical Functioning (eg, ability to carry out everyday tasks), Role Functioning (eg, relationships and ability to function in social roles), and Consequences of Bleeding (fear of having a bleed/what happens after you have a bleed). Here, Haemo-QOL-A results are presented for the 132 HIV-negative participants in total and by the participants' FVIII activity level at year 4. Other questionnaires will be included in the final presentation.

Results: Four years after treatment with valoctocogene roxaparvovec, the average Haemo-QOL-A Total Score increased by 6.2 points, an average improvement considered meaningful to people with severe HA (Table 1). Improvements were also seen for Physical Functioning (4.8 points), Role Functioning (5.9 points), and Consequences of Bleeding (9.2 points). At year 4, average Haemo-QOL-A Total Score increased by 6.3, 5.8, and 6.9 points for year 4 FVIII activity in ranges ≥40%, ≥5% to <40%, and <5%, respectively.

Conclusions: Valoctocogene roxaparvovec provides HRQOL improvements considered meaningful for people with severe HA over 4 years, even for participants with FVIII levels below 5% at year 4.

Table 1.

Haemo-QOL-A Total and domain scores before infusion and 4 years after infusion in 132 participants.[a]

	Before infusion	After 4 years	Change
Total Score			
Total Score reflects the overall impact of hemophilia on quality of life. Higher scores indicate better quality of life.			
Number of participants	130	125	123
Mean ± SD[b]	75.7 ± 16.7	82.4 ± 16.3	6.2 (95% CI,[c] 3.9-8.4)
Clinically meaningful difference?[d]			Yes
P-value[e]			<0.0001
Physical Functioning			
This domain reflects how hemophilia affects the ability to carry out everyday tasks. Higher scores indicate better quality of life.			
Number of participants	132	126	126
Mean ± SD	70.3 ± 20.8	75.6 ± 20.4	4.8 (95% CI, 2.1-7.5)
Clinically meaningful difference?			No
P-value			0.0005
Role Functioning			
This domain includes how hemophilia impacts ability to attend work or school. Higher scores indicate better quality of life.			
Number of participants	131	126	125
Mean ± SD	78.2 ± 17.8	84.9 ± 16.4	5.9 (95% CI, 3.3-8.4)
Clinically meaningful difference?			No
P-value			<0.0001
Consequences of Bleeding			
This domain includes fear of having a bleed/what happens after you have a bleed. Higher scores indicate better quality of life.			
Number of participants	132	126	126
Mean ± SD	73.6 ± 21.7	83.3 ± 21.0	9.2 (95% CI, 6.0-12.5)
Clinically meaningful difference?			Yes
P-value			<0.0001

[a]These results were based on the 132 participants who were HIV-negative and had observed data available before infusion or after 4 years. Two HIV-positive participants were excluded because enrollment of participants with HIV was suspended out of an abundance of caution for long-term liver health. The results include participants who started using regular prophylaxis again. The overall results are similar if participants who restarted regular prophylaxis had their data after returning to prophylaxis excluded.
[b]Mean ± SD, mean and standard deviation. The mean is the average score for the analysis population. The standard deviation is a measure of how much the scores vary between individual participants; the bigger the number, the more variability.
[c]The 95% CI (95% confidence interval) is a way to describe probability: there is a 95% chance that the true value is somewhere between the upper and lower bounds of the range estimated by the data.
[d]Experts have shown that a change of 5.5 for the Total Score, or 6.0 for domain scores, represents a clinically meaningful difference. For reference, please see Quinn J, et al. *Patient Relat Outcome Meas.* 2022;13:169-80.
[e]*P*-value. The *P*-value is a probability, calculated from a statistical test under the assumption that there are no differences before and after treatment, that describes how likely it is that the differences observed are purely due to chance. The smaller the value, the lower the likelihood. For this analysis, the *P*-value was based on a 2-sided t-test against 0. Because the analysis was not designed and adjusted to control for the possibility of false positive results, the *P*-values here are provided for descriptive purposes.

CO037

VALVULAR THROMBOSIS IN MVH PATIENTS OF THE EMERGENCY SALAM CENTRE COHORT

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Background and Aims: Mechanical heart valve (MHV) replacement is frequently required for patients with rheumatic heart disease. However, MHV requires long-life anticoagulation due to the associated valvular thrombosis (VT) and cardioembolism.
Methods: We report data from a prospective observational study conducted between August 2018 and September 2019 on MHV patients in the Salam Centre for Cardiac Surgery built in Khartoum by 'Emergency,' an Italian Non-Governmental Organization, to evaluate the occurrence of VT and the associated risk factors.
Results: We prospectively followed 3647 patients, and 38 patients (rate 1.04 x100 pt-years) had VT during follow-up. The time in therapeutic range (TTR) among patients without VT was 53% (IQR 37-67), and it was 43% (IQR 19-58) among patients with VT (p=0.04). Twenty-three over 38 patients (60.5%) were symptomatic, 18 (47.4%) had severe valvular stenosis, 24 patients (63.2%) had INR <2.0 at diagnosis, and 21 patients (55.3%) had been off warfarin for a long time: 3 patients for 1 week, 1 patient for 2 weeks, and 17 patients for >4 weeks (6 patients were off warfarin from 3-12 months). Ten were uncompliant to treatment, and 8 were pregnant women. Ten patients (26.3%) with VT had had a previous episode of VT, and 14 patients (36.8%) had 2 or more associated risk factors. Only in 6 cases were no associate risk factors found.
Conclusions: Among MHV patients on warfarin treatment with a sub-optimal quality of anticoagulation, the rate of VT is 1.04 x100 pt-years, and the principal associated risk factor for VT occurrence is warfarin withdrawal lasting more than one week.

CO038

PLASMA CONCENTRATIONS OF DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILATION AND DIFFERENT DEGREES OF OBESITY: A PROSPECTIVE COHORT STUDY

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Background: Obesity is associated with atrial fibrillation (AF), which increases the risk of thromboembolic stroke, requiring long-term anticoagulant therapy according to the CHADs-VASc score. International guidelines do not uniformly agree on how to manage anticoagulant therapy in obese patients with AF. While the current International Society of Thrombosis and Haemostasis (ISTH) guidelines recommend avoiding DOAC in patients with a BMI exceeding 40kg/m² or a body weight above 120kg; the consensus of experts from the European Society of Cardiology (ESC) recommend precaution when prescribing DOACs in patients with AF and obesity, especially if severe, although the prescription is possible.
Aim of the study: The aim of the present study was to evaluate the peak and trough plasma concentrations of DOACs in AF patients with obesity and to investigate factors associated with below-range trough DOAC plasma concentration.
Methods: This is a prospective single-centre study which consecutively enrolled AF obese patients between April 2023 and January 2024. Obesity was defined as body mass index (BMI)≥30 Kg/m². At baseline peak and trough DOAC plasma concentrations were assessed.
Results: 160 AF patients with obesity were enrolled. The mean age of the population was 73.2±9.1 years and 33.8% were female. The median BMI was 32.3 kg/m2 (I class of obesity). DOAC prescribed were apixaban (46.8%), rivaroxaban (21.8%), dabigatran (16.4%) and edoxaban (15.0%). 18.1% had below-range trough plasma concentrations. Patients with below-range trough plasma concentration had a higher history of stroke/TIA, were more frequently treated with edoxaban and dabigatran and had a higher BMI. At multivariable logistic regression analysis previous stroke/transient ischemic attack (Odds Ratio [OR] 3.948, 95% confidence interval [95%CI] 1.435-10.860) and BMI (OR 1.143 95%CI 1.039-1.258) were directly associated with below-range trough plasma concentration. Conversely, rivaroxaban (OR 0.186, 95%CI 0.041-0.837) and apixaban use (OR 0.283, 95%CI 0.092-0.875) were inversely associated with below-range plasma trough concentrations compared to dabigatran. No difference was observed between edoxaban and dabigatran.
Discussion: No studies have investigated if measurement of drug levels and dose adjustment based on laboratory coagulation parameters, improve the overall benefit of DOACs during long-term treatment. For example, the decision of dose reduction in case of higher-than-expected levels or of dose increase in case of lower-than-expected levels. However, laboratory assessment of drug exposure and anticoagulant effect may help clinicians in extreme body weight.
Conclusions: Our study has clinical implications. Firstly, it highlights the prevalence of below-range trough plasma concentrations in patients treated with DOAC and affected by obesity and AF. This is relevant due to the high thromboembolic risk of AF patients who are undertreated. In addition, our study may be useful to support the assessment of DOAC plasma concentration in routinary practice in obese patients with AF to reduce patients undertreatment and performing an early diagnosis.

Finally, our study suggests a potential association between type of DOAC and the risk of below-range trough plasma concentrations: rivaroxaban and apixaban may be useful to reduce this risk.

CO039

EX VIVO AND *IN VIVO* ANTIPLATELET EFFECTS OF ORAL ANTICOAGULANTS

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Background and Aims: All anticoagulants are expected to have an indirect effect on platelet function since they interfere with the generation or activity of thrombin, but the impact of non-vitamin K antagonist oral anticoagulants (NOACs) is still unclear. Both the direct thrombin inhibitor dabigatran and the direct factor (F) Xa inhibitors rivaroxaban and apixaban have been shown to inhibit thrombin-mediated effects and reduce the endogenous thrombin potential (ETP) in a concentration-dependent manner. Recent studies have also shown that they affect platelet aggregation induced by thrombin but also by tissue factor (TF). Nevertheless, the real impact of NOACs on platelet function has not yet been fully clarified and compared. Therefore, we conducted a comprehensive *ex vivo* and *in vivo* study aimed at assessing the effect of the four currently marketed NOACs on platelet function.
Methods: Blood samples from 20 healthy volunteers for each drug were incubated with increasing concentrations of NOACs (50, 150 and 250 ng/mL), in the range of those achieved in the plasma of patients during therapy. We evaluated generation of thrombin; light transmittance platelet aggregation in response to adenosine diphosphate (ADP), thrombin receptor-activating peptide (TRAP), human γ-thrombin and tissue factor (TF); generation of thromboxane (TX)B_2; and expression of protease-activated receptor (PAR)-1 and P-selectin on platelet surface. We also investigated the same parameters in 12 patients with atrial fibrillation treated with edoxaban (mean concentration 172 ng/mL).
Results: All NOACs concentration-dependently reduced thrombin generation compared with control, although with some differences between drugs in the measured parameters. ETP is the parameter more consistently affected by the addition of NOACs at different concentrations. Platelet aggregation induced by ADP and TRAP was not affected by the addition of any NOACs; conversely, platelet aggregation induced by thrombin was significantly reduced by the addition of dabigatran, and TF-induced platelet aggregation is inhibited by FXa inhibitors. TXB_2 generation was reduced by all NOACs, particularly at the highest concentrations. We found a concentration-dependent increase in PAR-1 expression after incubation with dabigatran, mainly at the highest concentrations, but not with FXa inhibitors; P-selectin expression was not changed by any drugs. The antiplatelet effect of edoxaban observed in *in vivo* treated patients is somewhat less pronounced, probably due to the smaller number of subjects involved, but still in line with what has been observed previously. It significantly reduced TF-induced platelet aggregation but did not affect platelet aggregation induced by other agonists. We observed a trend towards reduction in serum TXB_2 concentration, though not significant. Similarly to *ex vivo* observation, edoxaban reduced thrombin generation compared with control, mainly affecting lag time and time to peak parameters. PAR-1 and P-selectin expressions were not significantly changed by edoxaban in patients compared with control.
Conclusions: Treatment with the NOACs is associated with measurable *ex vivo* changes in platelet function, with some differences among the four drugs, arguing for antiplatelet effects which may, in turn, lead to the delayed/reduced formation of coagulation complexes reinforcing their antithrombotic potential.

CO040

EVALUATION OF SAFETY AND EFFICACY OF ANTICOAGULATION TREATMENT IN PATIENTS WITH SPLANCHNIC VEIN THROMBOSIS: THE SAPIENT STUDY

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Background and Aims: Splanchnic vein thrombosis (SVT) is a potentially life-threatening disease that can occur in cirrhotic and non-cirrhotic patients. Anticoagulation with heparins and vitamin K antagonists (VKAs) is the mainstay of treatment. Recent studies have

suggested that direct oral anticoagulants (DOACs) may offer a viable alternative in these settings. However, data on the safety and efficacy of DOACs are still limited, especially in cirrhotic patients. The aim of the study is to prospectively evaluate the occurrence of bleeding and thrombotic events in patients with SVT receiving anticoagulant therapy.

Methods: This is a prospective, single-centre, observational study. Consecutive adult cirrhotic and non-cirrhotic patients referred to the Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome for SVT and requiring anticoagulant therapy are eligible for inclusion. Exclusion criteria include splanchnic vein tumor thrombosis and the absence of anticoagulant therapy. Enrolled patients will be observed for at least 24 months. The primary outcome is a composite of major bleeding, as defined by the International Society of Thrombosis and Hemostasis (ISTH), and recurrent thrombotic events (any major thrombosis involving deep veins at usual or unusual sites and any major arterial thrombosis) during anticoagulant therapy. Among secondary outcomes are evaluated: incidence rate (IR) of progression, stability, and regression of SVT; IR of recurrent superficial venous thrombosis and clinically relevant non-major bleeding events, according to ISTH definition, during anticoagulant therapy. Regarding SVT diagnosis, doppler ultrasound is usually the first-line approach, but contrast-enhanced CT or MR angiography is recommended for confirmation. SVT patients receive anticoagulant therapy for at least 6 months according to current guidelines. With regard to the extension of anticoagulant treatment beyond 6 months, the current recommendations are followed, considering a permanent underlying prothrombotic state and balancing the benefits of preventing recurrence and increasing survival with the risk of bleeding.

Results: The local Ethics Committee approved the study at the end of October 2023; enrollment started in mid-November. Ninety-eight patients were enrolled until 31 March 2024, including twenty-nine (29.6%) cirrhotic and sixty-nine (70.4%) non-cirrhotic patients. Overall, fifty patients (51%) were taking DOACs at the time of enrollment, while the remaining (49%) were taking VKAs or a parenteral anticoagulant. Details on the type and dosage of anticoagulant therapy, and the different etiologies of disease in non-cirrhotic SVT, will be reported in the following analysis.

Conclusions: This is a prospective observational study evaluating the safety and efficacy of anticoagulation therapy in patients with SVT in the DOAC era. The first interim analysis results, in which all patients enrolled until 31 March 2024 will have at least 6 months of follow-up, will be presented during the National Congress.

CO041

LONG-TERM ANTICOAGULANT TREATMENT OF PATIENTS WITH VENOUS THROMBOEMBOLISM AT HIGH RISK FOR RECURRENCE

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Background and Aims: Venous thromboembolism (VTE) is associated with high risk of recurrence (HRR). Long term anticoagulant treatment is recommended for HRR patients. Treatment with low-dose Direct oral anticaoagulant (DOAC) apixaban and rivaroxaban has been investigated among patients deemed to carry equipoise between bleeding risk of treatment and the thrombotic risk. However, no HRR patients have been included in these trials. In the frame of the START2 Register, we performed a retrospective observational study to evaluate the management of HRR patients enrolled in the study. We defined HRR patients all subject with: 1) at least 2 episodes of proximal deep vein thrombosis (DVT) +/-Pulmonary Embolism (PE) or isolated PE; or 2) with severe thrombophilia (AT, PC or PS deficiency; homozygous for factor V Leiden or prothrombin mutation, double etherozygous for both mutations); or 3) with proximal DVT +/- PE and active inflammatory bowel disease (IBD).

Methods: 437 patients were enrolled in HRR START Register. Results the follow-up is available for 237 patients, median age 65 years, 59.5% males. The index event was treated in about 70% of patients with DOAC, the remaining patients were treated with VKA or LMWH/Fondaparinux. After a median time of 1,3 months of standard treatment, 218/237 patients (92%)

were shifted to extended treatment with low dose DOAC, 137 of them (62.8%) on apixaban 2.5 mg bid, and 81 (3.2%) on rivaroxaban 10 mg od. During the 574 patient-years (pt-years) of follow up 1 patient on apixaban had post-traumatic sub-dural hematoma (rate 0.2 x100 pt-yrs); 4 patients (rate 0.7 x100 pt-yrs) had VTE recurrence (1 on rivaroxaban, 3 on apixaban).
Conclusions: These results seem to confirm the safety and efficacy of low-dose DOAC also in HRR patients.

CO042

ANTICOAGULANT TREATMENT FOR ISOLATED DISTAL DEEP VEIN THROMBOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The optimal therapeutic management of Isolated Distal Deep Vein Thrombosis (IDDVT), both in terms of the need for and duration of anticoagulation, remains uncertain.
Aims: We performed a meta-analysis of randomized and cohort studies in patients with IDDVT to assess the clinical benefit of anticoagulant therapy *versus* no therapy and prolonged anticoagulant treatment *versus* short-term treatment.
Methods: We performed a systematic search of electronic databases up to March 2024 to identify all available studies on anticoagulant therapy in IDDVT. Efficacy outcomes of this analysis were recurrent venous thromboembolism (VTE), pulmonary embolism (PE), proximal progression and post thrombotic syndrome (PTS); major bleeding and clinically relevant non-major bleeding were also analyzed as safety outcomes. The outcomes incidence was stratified by the duration (Short, <6 weeks of therapy; Long, 6-12 weeks of therapy; extended, >12 weeks of therapy; mixed, mixed duration of therapy), dose of anticoagulant therapy (therapeutic, intermediate, prophylactic) and by the classes of risk. Pooled relative risks (RRs) with corresponding 95% confidence interval (CI) were calculated.
Results: Of the 1914 articles retrieved from the search, 49 studies met the inclusion criteria and were included in the analysis, for a total of 11871 patients. Patients who received anticoagulation had a non-significantly lower rate of recurrent VTE compared to those who did not receive anticoagulation (11871 patients), either for a short (RR 0.21, 95% CI 0.03-1.60), long (RR 0.40, 95% CI 0.21-1.36) or mixed (RR 0.56, 95% CI 0.28-1.11) duration, without increasing the risk of major bleeding (8743 patients; RR 0.15, 95% CI 0.02-1.22 for short duration; RR 0.29, 95% CI 0.14-0.58 for long duration). Short-term treatment was associated with a significantly higher rate of recurrent VTE (RR 2.72, 95% CI 1.19-6.23) and proximal progression of thrombosis (RR 3.86, 95% CI 1.77-8.43) as compared to prolonged anticoagulant therapy. No difference in the risk of PE between treated and untreated patients was observed.
Conclusions: A trend toward fewer recurrence events was observed with the use of anticoagulant therapy in patients with IDDVT, without an increased risk of major bleeding. When anticoagulation is prescribed, long-term duration (for more than six weeks) should be preferred over shorter duration to prevent recurrent VTE and proximal extension of IDDVT.

CO043

EXTENDED TREATMENT WITH FULL- OR REDUCED-DOSE DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH CANCER-ASSOCIATED THROMBOSIS: RESULTS FROM THE ITALIAN MULTICENTER RETROSPECTIVE COHORT STUDY ONCO-VTE

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Introduction: Venous thromboembolism (VTE) recurrence rates in cancer patients remain high even beyond six months after the initial thromboembolic episode. Evidence on efficacy and safety of reduced-dose Direct Oral Anticoagulants (DOACs) for secondary prevention of Cancer Associated Thrombosis (CAT) is limited. The Onco-VTE study aims to address this gap by gathering real-life data on CAT extended treatment with full and reduced DOACs.
Methods: Patients were retrospectively enrolled from four Italian centers, in presence of a VTE event and active malignancy or history of cancer in the previous two years. Enrolled patients were divided into two cohorts based on the dose of DOAC they received after sixth months from the VTE index episode. Required minimum follow-up for inclusion was six months, unless a censoring event occurs, such as death, VTE recurrence,

major bleeding, discontinuation of DOAC therapy, or switching to another anticoagulant.

Results: Among the 603 enrolled patients, 381 (63.2%) received reduced-dose, while 222 (36.8%) received full-dose DOACs. Baseline characteristics are reported in Table 1. The median follow-up time was 413.9±329.0 days. The incidence rates of thrombotic and hemorrhagic events were calculated per 100 person-years. VTE recurrence rates were 3.3 (95% Confidence Interval, 95%CI 2.0-5.5) in the reduced-dose and 2.5 (95%CI 1.1-5.7) in the full-dose cohort. Major bleeding occurred at rates of 0.9 (95%CI 0.3-2.3) and 0.8 (95% CI 0.2-3.4) in the reduced and full-dose cohorts, respectively. Clinically Relevant Non-Major Bleedings were observed at rates of 3.3 (95%CI 2.0-5.5) and 3.8 (95%CI 2.0-7.3) in the reduced and full-dose cohorts, respectively. To overcome the impact of a significant prescription bias in interpreting the collected evidence, a multilevel logistic regression model adjusted for center of enrollment was employed to identify variables influencing dose choice. This model revealed a lower probability of receiving a reduced-dose DOAC in patients with history of previous stroke (Odds Ratio, OR 0.1, 95%CI 0.02-0.9, p=0.04), diabetes (OR 0.5, 95%CI 0.2-0.9, p=0.03), atrial fibrillation (OR 0.2, 95%CI 0.1-0.7, p=0.01), tolerance of therapeutic anticoagulation during the acute phase (OR 0.4, 95%CI 0.2-0.6, p=0.0005). On the other hand, reduced dose DOACs were preferentially prescribed in patients with cerebral metastases (OR 4.0, 95%CI 1.3-12.8, p=0.02).

Table 1.

	Reduced-dose cohort (n=381)	Full-dose cohort (n=222)	p
Patient's characteristics			
Male, n (%)	75 (19.7)	88 (39.6)	<0.0001
Female, n (%)	306 (80.3)	134 (60.4)	
Age, years, mean ± SD	64.0 ± 12.2	67.8 ± 12.1	0.0002
Weight, kg, mean ± SD	70.2 ± 15.4	74.7 ± 16.8	0.001
eGFR acc. CG, mL/min/m², mean ± SD	79.1 ± 29.1	73.3 ± 26.1	0.01
History			
Previous VTE, n (%)	47 (12.3)	35 (15.8)	0.24
Previous MB, n (%)	8 (2.1)	5 (2.2)	0.90
Previous stroke, n (%)	3 (0.8)	5 (2.2)	0.13
Medical comorbidities			
Atrial fibrillation, n (%)	6 (1.6)	14 (6.3)	0.002
Chronic coronary syndrome, n (%)	7 (1.8)	11 (4.9)	0.03
Heart failure, n (%)	10 (2.6)	13 (5.9)	0.04
Lower extremity peripheral artery disease, n (%)	7 (1.8)	7 (3.1)	0.30
Carotid artery disease, n (%)	16 (4.2)	8 (3.8)	0.72
Arterial hypertension, n (%)	179 (47.0)	119 (53.6)	0.12
Diabetes, n (%)	41 (10.8)	34 (15.3)	0.10
Cancer-associated characteristics			
Metastatic cancer, n (%)	271 (71.1)	102 (45.9)	<0.0001
Cerebral metastases, n (%)	28 (7.3)	5 (2.2)	0.008
Active cancer, n (%)	348 (91.3)	205 (92.3)	0.66
History of cancer, n (%)	33 (8.7)	17 (7.6)	
VTE index event characteristics			
Usual VTE, n (%)	263 (69.0)	191 (86.0)	<0.0001
Unusual VTE, n (%)	118 (31.0)	31 (14.0)	
Pulmonary embolism	174 (45.7)	129 (58.1)	0.003
Catheter-related thrombosis	93 (24.4)	13 (5.8)	<0.0001
Acute treatment with therapeutic anticoagulant dose	263 (69.0)	189 (85.1)	<0.0001

Baseline characteristics of study population. eGFR: estimated Glomerular Filtration Rate. CG: Cockcroft-Gault. MB: major bleeding. SD: Standard Deviation. VTE: venous thromboembolism.

Conclusions: The retrospective nature of the study determined the presence of a prescription bias, with significant differences between full- and reduced-dose cohorts in terms of type of thromboembolic event, cancer, and comorbidities. This confounding does not allow the direct comparison of the two therapeutic regimens. On the other hand, number of events and related incidence rates in both full- and reduced-dose cohorts are in line with previous literature on the full-dose DOACs extended treatment of CAT. Therefore, this experience appears to be reassuring regarding the possibility of using reduced-dose DOACs in the extended treatment of VTE in this population. More importantly, the documented incidence rates could also be the result of a careful clinical selection of patients, who could have benefited from individualization of therapy. A multilevel logistic regression model identified several predictive clinical variables influencing the prescription of full or reduced dose DOACs. This model could aid in tailoring extended DOAC treatment in cancer patients.

CO044

PATIENTS' CHARACTERISTIC AND LONG-TERM OUTCOMES IN A SINGLE CENTER COHORT OF MPN PATIENTS WITH SPLANCHNIC VEIN THROMBOSIS

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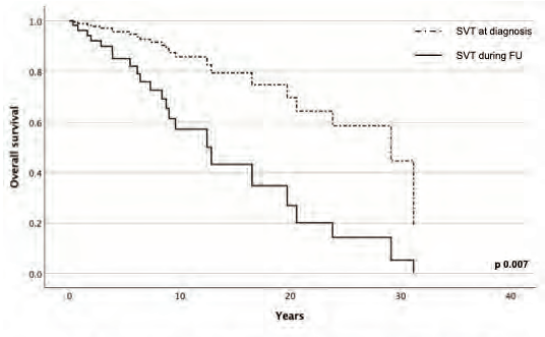
Background: In the last decades, myeloproliferative neoplasms (MPNs) emerged as a leading cause of splanchnic vein thrombosis (SVT). The JAK2V617F mutation, the most frequent driver mutation in MPN, showed a strong association with the development of SVT. About 5% of patients with portal vein thrombosis (PVT) and 25–50% with Budd-Chiari syndrome (BCS) either have MPN at baseline or are subsequently diagnosed with MPN. MPN-SVT patients are predominantly younger (40-45 y), female (65–80%) and have shortener survival compared to MPN without SVT. This excess of mortality has been attributed either to a higher frequency of fatal hemorrhage, liver failure, and second malignancies, or to complications due to MPN. We analyze characteristics and long-term outcomes of a large cohort of MPN-SVT patients diagnosed in our Department and followed for a median time of 15y.

Methods: We studied 59 MPN-SVT patients diagnosed and followed in our Department in the last four decades (18 M, 41 F, median age at MPN diagnosis 39.9y, median follow-up - FU 15.8y), 21 (35,6%) diagnosed with Polycythemia Vera (PV), 34 (57,6%) with Essential thrombocythemia (ET), 5 (8,5%) with undefined MPN. JAK2 mutational status was available in 39 patients (66,1%), all but one tested patients carry

JAK2V617F mutation. MPN diagnosis has been performed according to current criteria at time of observation and, when available, revised to the most recent WHO criteria. 24 patients (40,7%) died during follow-up: 7 due to MPN progression (5 myelofibrosis, 2 acute leukemia), 5 to SVT complications (2 liver failure, 3 second malignancy), 2 to fatal hemorrhage, 2 to pulmonary embolism and 8 to other/unknown causes. Survival analysis and curve were prepared with Cox regression model.

Results: Among our 59 MPN-SVT patients stratified according to SVT type (23 BCS and 36 PVT), no difference has been reported in distribution of gender, type of MPN, known inherited thrombophilia and time of SVT occurrence (at MPN diagnosis/during follow-up). BCS patients were younger both at diagnosis of MPN (p=0,001) and at time of thrombosis (p <0,001). In 43 patients (72,8%; 15 BCS, 28 PVT) occurrence of SVT leads to MPN diagnosis, the other 16 developed SVT during MPN FU, after a median of 9,4y. Stratifying patients according to time of SVT occurrence, patients who developed SVT during FU showed a significant worse survival, adjusted for age at SVT, type of SVT and presence of inherited thrombophilia, compared to those presenting with SVT (Figure 1, p 0,007). Among patients with SVT occurred during FU, 4 out of 9 died for MPN progression (after a median of 14,7 y from MPN diagnosis), 3 for hepatic complications, 2 of unknown causes. No difference has been observed in distribution of causes of death (MPN or SVT related) between patients with SVT at diagnosis or during FU.

Conclusions: The strong association between SVT and MPN has been widely described, mainly with JAK2 positive MPNs. Our series has one of the longest FU reported in the literature. We observed worse post-SVT survival in patients with SVT during FU compared to those presenting with thrombosis. The hypothesis underlying this observation is that patients who develop SVT during FU may have an underlying disease that is more difficult to control even if already on therapy, although it cannot be excluded that it is also a consequence of the natural history of the underlying MPN. Further studies are necessary to investigate this observation.



Overall post-SVT survival in MPN patient presenting with SVT and those who develop SVT during FU. *Adjustment variables in Cox regression model: age at time of SVT, presence of inherited thrombophilia, type of SVT (BCS or PVT)*

Figure 1.

CO045

LONG-TERM ANTITHROMBOTIC PROPHYLAXIS AFTER MULTIPLE MYELOMA-RELATED VENOUS THROMBOEMBOLISM: A MONOCENTER RETROSPECTIVE STUDY ON SAFETY AND EFFECTIVENESS OF DIFFERENT STRATEGIES

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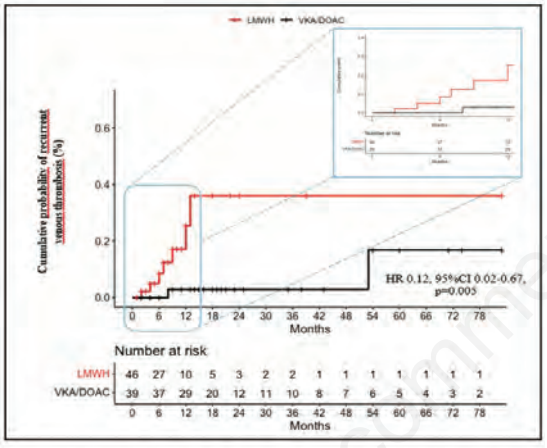
Background and Aims: Multiple Myeloma (MM) increases the risk of developing blood clots, especially during treatment with immunomodulatory drugs (IMID). Venous thromboembolism (VTE) can occur in up to 10% of MM patients, even with antithrombotic prophylaxis. It is unclear which long-term secondary antithrombotic prophylaxis is best. This study is a retrospective monocenter analysis of patients with MM, comparing different long-term secondary antithrombotic strategies after VTE to evaluate their effectiveness and safety.

Methods: We have gathered data on 95 patients with MM who have experienced VTE events at any phase of the disease. For the purpose of our analysis, we have only included patients with deep venous thrombosis and pulmonary embolism (DVT/PE), excluding 10 patients with superficial vein thrombosis. Our study focused on the secondary antithrombotic prophylaxis, which involves the use of low molecular weight heparin (LMWH), vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) beyond the treatment of acute VTE. Our primary outcomes for this study were venous thrombotic recurrence and major bleedings (MB) or clinically relevant non-major bleeding (CRNMB).

Results: We analyzed 85 patients with MM (M/F 47/38) who have experienced DVT and/or PE. The median age was 65 years, ranging from 40 to 85 years. After treating the acute phase of DVT/PE, 47 patients received LMWH, 10 patients VKA, and 28 patients DOACs. The anticoagulation was discontinued in 38 patients after a median of 6 months (range 1-22) due to the absence of predictors of thrombotic recurrence (the patients had had distal or post-surgical DVT or central-venous catheter-related DVT or received IMID-free therapy): we recorded 4 DVT/PE with an incidence rate (IR) of 2.5/100 pt-yrs. During active anticoagulation, we recorded 8 DVT/PE recurrences (6 in LMWH and 2 in VKA). The IR per 100 pt-yrs incidence of DVT/PE recurrence was higher in the LMWH group compared to the VKA group (15.6 *vs.* 6.9, p=0.33) and DOACs group (0, p=0.003). There was also a significant difference between VKA and DOACs (p=0.05). Patients receiving oral VKA and DOACs had a significantly lower cumulative probability of recurrent DVT/EP in comparison with LMWH (HR 0.12, 95% C.I. 0.02-0.67, p=0.005). The two recurrences that occurred in the oral anticoagulation group happened in the VKA arm. This difference was particularly signif-

icant during the first 12 months of anticoagulation (Figure). We recorded 5 MB (4 in LMWH and 1 in VKA) and 5 CRNMB (2 in LMWH and 3 in VKA). We found no significant differences in bleeding risk between patients treated with oral anticoagulants and LMWH. However, the bleeding risk seemed to be lower during oral anticoagulant treatment (HR 0.32, 95% C.I. 0.008-1.33, p=0.1). Our multivariable analysis included male sex, inherited thrombophilia, personal history of VTE, superficial vein thrombosis during MM, first thrombosis after the first year from MM diagnosis, use of IMID, and oral anticoagulation. Only the latter was an independent protective factor for venous thrombosis recurrence (HR 0.21, 95% C.I. 0.05-0.81, p=0.02).

Conclusions: Although this study has some limitations due to its retrospective design and small sample size, our analysis revealed that oral anticoagulation is more effective than LMWH in preventing venous thrombotic recurrence without a significant increase in bleeding risk. In our experience, DOACs appear to be more effective and safer than VKA.



Cumulative probability of recurrent venous thrombosis in oral anticoagulants (VKA/DOAC) and LMWH. The upper box shows the detail of the first 12 months of anticoagulation.

Figure 1.

CO046

INCIDENCE OF SUPERFICIAL VEIN THROMBOSIS IN PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS AND RISK OF RECURRENCE

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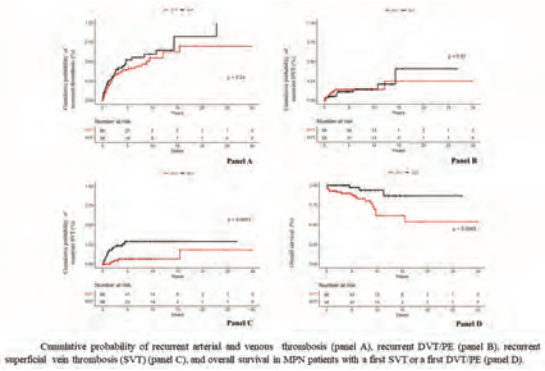
Background and Aims: Superficial vein thrombosis (SVT) is a relatively common with an incidence rate (IR) of 0.06 to 0.15 per 100 person-years in the general population. Despite its benign nature, individuals with a history of SVT face a 5-fold increased risk of subsequent venous thrombosis according to the MEGA study. Moreover, SVT is a paraneoplastic condition, and active cancer is associated with a 2-fold increased risk of venous recurrence after SVT. Precise data about the incidence of SVT in MPN are lacking. Our study aims to ascertain the incidence of SVT in the MPN patients, and its risk of recurrence, in comparison with MPN patients with deep venous thrombosis (DVT).

Methods: We have carried out a retrospective analysis of all MPN patients who were under observation at our center from 1978 to 2023. We identified those patients with either an MPN-related SVT or an MPN-related DVT as their initial thrombotic event. Thrombosis was classified as MPN-related if it happened within two years before diagnosis of MPN.

Results: We identified 58 cases of first SVT among 1,390 MPN patients, with an IR of 0.55 per 100 pt-years over 10.577 observation years. Comparing this with 86 patients who experienced a first DVT (IR 0.81 per 100 patient-years), the SVT IR was significantly lower than the DVT IR (p=0.02). Differently from patients with DVT, those with SVT did not receive long-term treatment with oral anticoagulants after a course of low molecular weigth heparin. Thrombotic recurrence occurred in 32 (55.2%) SVT patients and 34 (39.5%) DVT patients, resulting in an IR per 100 pt-years of 12.3 and 8.8, respectively, (p=0.18). Concerning venous recurrences, SVT patients exhibited a significantly higher IR of recurrence in the venous district per 100 pt-years (IR 10.8) compared to patients with a first DVT (IR 5.20, p=0.03). The IR per 100 pt-years of recurrent DVT was 3.5 after the first SVT (n=9, 15.5%) and 2.9 after the first DVT (n=11, 12.8%), with no difference between the two groups (p=0.66); on the other hand, the IR per 100 pt-years of recurrent SVT was significantly higher after the first SVT (IR 5.8) than after the first DVT (IR 1.30, p=0.002). The two groups had no significant differences regarding the IR of arterial or unusual site thrombosis (data not shown). Neither there was a significant difference between patients with first SVT or first DVT as regards the cumulative probability of overall recurrent thrombosis (hazard ratio HR 1.34, 95%CI 0.83-2.17, p=0.24) [Figure 1, Panel A] or recurrent DVT (HR 1.02, 95%CI 0.42-2.46, p=0.97) [Figure 1, Panel B]. Conversely, there was an higher HR of a second SVT in the SVT group compared to the DVT group (HR 4.56, 95%CI 1.65-12.59, p=0.001) [Figure 1, Panel C]. Finally, the SVT group had a higher survival rate than the DVT group (HR 0.21, 95%CI 0.06-0.73, p=0.007) [Figure 1, Panel D].

Conclusions: The incidence of SVT in MPN patients seems to be increased compared to the general population. Patients with a first SVT show a risk of a second DVT as high as those with a first DVT; moreover, they are more prone to recurrence in the superficial veins. The two cohorts are not comparable given the absence of long-term anticoagulation in patients with SVT. However, a first SVT predicts a second event involving deep veins in a not negligibile portion of patients as high

as 15%, with an IR of 3.5 per 100 pt-years; therefore special attention should be paid to those patients.



Cumulative probability of recurrent arterial and venous thrombosis (panel A), recurrent DVT/PE (panel B), recurrent superficial vein thrombosis (SVT) (panel C), and overall survival in MPN patients with a first SVT or a first DVT/PE (panel D).

Figure 1.

CO047

ANTITHROMBOTIC PROPHYLAXIS AFTER VENOUS THROMBOEMBOLISM IN PATIENTS WITH PH-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS TREATED WITH VITAMIN K ANTAGONISTS OR DIRECT ORAL ANTICOAGULANTS: A PROPENSITY SCORE-MATCHED ANALYSIS

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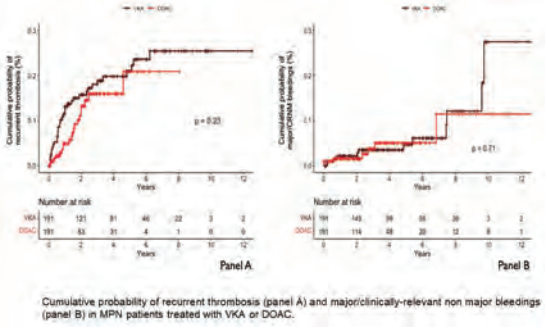
Background and Aims: Individuals with Philadelphia-negative Myeloproliferative Neoplasms (MPN) are at a higher risk of recurrence after venous thromboembolism (VTE). Data regarding the effectiveness and safety of vitamin K antagonist (VKA) and direct oral anticoagulants (DOAC) for secondary VTE prophylaxis in MPN patients are available; however, a direct comparison has never been made.

Methods: The study participants were selected from the databases of 4 distinct retrospective studies conducted by the same authors since 2008 across various specialized European centers (*De Stefano V et al., Haematologica 2008; De Stefano V et al., Blood Cancer J 2016; De Stefano V et al., Leukemia 2016; Barbui T et al., Leukemia 2021*). Inclusion criteria comprised patients who experienced an MPN-related VTE and underwent secondary antithrombotic prophylaxis, either with VKA or DOAC. To ensure homogeneity between the two patient cohorts, Propensity Score Matching (PSM) was employed with a 1:1 ratio. Covariates used in the matching process included sex, age at diagnosis and at the occurrence of the index thrombosis, site of thrombosis (common *vs* uncommon), and the cytoreductive therapy administered.

Results: Six hundred eighteen subjects met the inclusion criteria (382 on VKA and 236 on DOAC). After PSM, two distinct subgroups, each consisting of 191 patients, were formed for each treatment. The median age at the time of index thrombosis was 65.6 years (range 20-94), with initial thrombotic events predominantly occurring at typical sites [deep vein thrombosis (DVT)=116 (30.3%), pulmonary embolism (PE)=77 (20.2%), DVT/PE=62 (16.2%)]. Splanchnic vein thrombosis occurred in 91 (23.8%) patients, while Budd-Chiari and cerebral vein thrombosis occurred in 19 (5.0%) and 17 (4.5%) patients, respectively. The cumulative observation time for the entire cohort was calculated to be 1,434 years (median 3.12 years), during which 57 thrombotic recurrences were documented, comprising 42 venous and 15 arterial events, resulting in an incidence rate (IR) of 4.0 per 100 pt-years. The annualized IR per 100 pt-years was 4.3 in the VKA group and 3.4 in the DOAC group, with no statistically significant differences observed (p=0.4). The 1-, 3-, and 5-year cumulative probabilities of recurrence were 12.6%, 18.1%, and 21% in the VKA group and 5%, 16%, and 20.9% in the DOAC group, respectively (HR 0.72, 95%CI 0.41-1.24, p=0.2) [Figure 1, Panel A]. Accounting for competing risks, patients on DOAC, compared to those on VKA, exhibited similar cumulative incidences of both venous (p=0.7) and arterial recurrence (p=0.4). In the entire cohort, 19 (4.97%) patients experienced major or clinically relevant non-major (CRNM) bleeding during anticoagulant treatment [VKA=12 (6.3%), DOAC=7 (3.7%)], with an IR per 100 pt-years of 1.4 in the VKA group and 1.2 in the DOAC group (p=0.7). The 1-, 3-, and 5-year cumulative probabilities of major/CRNM bleedings were 2.2%, 3.5%, and 4.7% in the VKA group and 1.6%, 3.8%, and 5.0% in the DOAC group, respectively (HR 0.84, 95%CI 0.33-2.15, p=0.7) [Figure 1, Panel B].

Conclusions: Our study indicates that using DOAC following VTE in MPN patients is both effective and safe as VKA, with the limitations of a retrospective observation. However, the use of PSM reduces the confounding effects. Although the effectiveness and safety of antithrombotic prophylaxis after VTE are largely unsatisfactory in MPN patients, demonstrating the equivalence of DOAC to VKA can significantly improve their quality of life.



Cumulative probability of recurrent thrombosis (panel A) and major/clinically-relevant non major bleedings (panel B) in MPN patients treated with VKA or DOAC.

Figure 1.

CO048

ENOXAPARIN FOR CENTRAL VENOUS CATHETER ASSOCIATED UPPER EXTREMITY DEEP VEIN THROMBOSIS IN CANCER PATIENTS

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Background and Aims: The incidence of upper extremity deep vein thrombosis (UEDVT) in association with use of central venous catheters in cancer patients is a frequent finding. The optimal duration of anticoagulation therapy for this type of UEDVT is clinically relevant, but the evidence is lacking.
Methods: We investigated whether a 12-week treatment with low-molecular-weight heparin (LMWH) can was effective and safe as a longer treatment in cancer patients with catheter related UEDVT (CR-UEDVT). In this retrospective study, 204 patients with CR-UEDVT received enoxaparin 1 mg/kg subcutaneously twice a day for 4 weeks followed by 1.5 mg/kg subcutaneously once a day for 8 weeks, whereas 142 patients received enoxaparin 1 mg/kg subcutaneously twice a day for 4 weeks followed by 1.5 mg/kg subcutaneously once a day for at least six months. The primary end-point was the composite measure of recurrent venous thromboembolism (VTE). The primary safety outcome was the combined rate of major bleeding and clinically relevant non-major bleeding.
Results: The study population has a mean age of 57.5±16.3 (female 55.5%); metastatic cancer was present in 165 (47.7%) patients. During a mean follow-up of 770±556 days, there were 95 deaths (27.5%). The primary efficacy outcome occurred in 58 patients (16.8%): UEDVT in 49 cases (14.2%), pulmonary embolism in 5 cases (1.4%), portal thrombosis in 2 cases (0.6%), and lower extremity DVT in 2 cases (0.6%). The primary efficacy outcome occurred in 29 (14.2%) patients receiving 12-week LMWH and in 29 (20.4%) patients receiving long term LMWH with a hazard ratio of 0.65 (95%CI: 0.37-1.14, p=ns). Ten patients had clinically relevant bleedings (4.6%) in the 12-week LMWH group *vs.* eight (5.6%) in long term LMWH group (p=0.76).
Conclusions: Enoxaparin for 12 weeks seems to be effective as enoxparin for more than 6 months in avoiding thrombosis recurrences in patients with CR-UEDVT.

CO049

THE ROLE OF ANTI-EMICIZUMAB ANTIBODIES AND THEIR CLINICAL RELEVANCE

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Background and Aims: The development of anti-drug antibodies (ADAs) in patients treated with emicizumab is a rare event. ADAs can be transient, without clinical significance, or can dramatically influence the therapeutic response. Their clinical implications are not fully clarified. ADAs detection is complicated by the presence of circulating drug. The aim of this study is to describe the prevalence of anti-emicizumab antibodies and their clinical relevance in the Milan cohort.
Methods: 70 children and adults affected with haemophilia A, with and without FVIII inhibitor, have been switched to emicizumab at the Haemophilia and Thrombosis Center in Milan. Clinical information including events of spontaneous bleeding were collected; laboratory evaluation such as aPTT, emicizumab levels, and ADAs detection were performed at several time points and when patient had bleeding symptoms.
Results: Four out of sixty-seven (5.9%) studied patients, developed ADAs with reduced emicizumab levels (Table 1). ADAs have been developed at different exposure days, from 4 to >200. No correlation was observed between ADAs and bleeding symptoms. The minimum level of emicizumab reported was 17µg/mL with no bleeding symptoms. No correlation between emicizumab level and bleeding events was found.
Conclusions: Our experience confirms that there is no need of a regular detection of the anti-emicizumab antibodies in patients with no bleeding. Moreover, in our cohort we found no correlation between clinical manifestations and emicizumab levels, at least with emicizumab concentration >17µg/mL. Further investigation, as aPTT, emicizumab concentration and anti-drug antibodies, should be reserved only in patients with loss of drug efficacy or bleeding symptoms.

Table 1.

Patient ID	1	2	3	4
Age (years)	10	75	61	11
FVIII inhibitor	yes	yes	yes	no
Dosage/scheme	1 mg/kg/2 weeks	1.5 mg/kg/week	1.5 mg/kg/week	1.5 mg/kg/week
N. of exposures at ADAs occurrence (doses)	9	9	>200	4
Emicizumab at ADAs occurrence (µg/mL)	25.8	28.3	22.5	49.1
Minimum emicizumab concentration reached (µg/mL)	25	17	18.9	31.7
aPTT ratio	0.82	0.75	0.86	0.78
Bleeding	no	no	spontaneous at joint at >200 doses	spontaneous at joint and muscle at 4th dose
Emicizumab discontinuation	no	no	no	yes

CO050

JOINT HEALTH AND QUALITY OF LIFE SCORES FROM BASELINE TO ONE YEAR AFTER SWITCHING TO EMICIZUMAB

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Background and Aims: Emicizumab was the first non-replacement product approved for prophylaxis of patients with hemophilia A (HA), with and without inhibitors. The efficacy and safety of emicizumab were established by several clinical studies and real-world reports, although less is known concerning the effect on joint health and quality of life. Given this background, the aim of our study was to evaluate joint health and quality of life before switching and one year after emicizumab prophylaxis.
Methods: Consecutive HA patients starting emicizumab were enrolled in a prospective cohort study. Joint health was assessed with the Hemophilia Joint Health Score (HJHS version 2.1) and the Hemophilia Early Arthropathy Detection with Ultrasound Score (HEAD-US). The synovitis total score was assessed with the HEAD-US. Quality of life was assessed only in adults with the 5-level EQ-5D version tool (EQ-5D-5L). All scores were collected by the same operators before switching to emicizumab and 12 months after. Paired-samples T-test was performed before and after switching for the HJHS, total HEAD-US and total synovitis score.

	Any problem Before	Any problem After
Mobility	8	5
Looking after myself	2	0
Daily activities	1	2
Pain or Discomfort	12	4
Anxiety or sadness	9	4

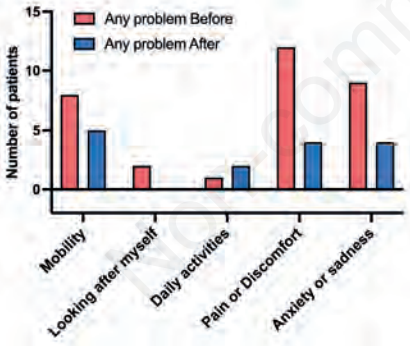

Figure 1.

Results: Twenty-five patients with HA on emicizumab prophylaxis were enrolled, 5 children (median age 4 years, IQR 3-8) and 20 adults (median age 43, IQR 33-50). Three adult patients had inhibitor and 7 adult patients had one or more prosthetic joints. Fourteen adult patients had synovitis according to the HEAD-US score before emicizumab switch and in 10 out of 14 patients the total synovitis score diminished after 1 year (in the whole population median synovitis score before switching 1, IQR 0-1; median synovitis score after switching 0, IQR 0-1; p-value <0.01). The osteochondral and subchondral bone damage score did not change before and after one year of prophylaxis with emicizumab. The median HJHS score was 15 before switching (IQR 4-23) and 11 after 1 year (IQR 2-20), p-value 0.07. Regarding the EQ-5D-5L tool, nine patients reported "any problem" in the anxiety/sadness domain before switching and 5 out of 9 changed to "no problem" after 1 year of emicizumab prophylaxis (Figure 1). Twelve patients reported pain or discomfort before switching and only 4 after switching. Eight patients reported "any problem" in the mobility domain before switching and 5 patients after.
Conclusions: In conclusion, the total synovitis score diminished in 10 out of 14 patients after 12 months of emicizumab prophylaxis. Based on the quality-of-life assessment tool, 4 out of 5 domains improved after switching to emicizumab prophylaxis.

CO051

INHIBITORS IN NON-SEVERE HEMOPHILIA A: AN UNDERESTIMATED ISSUE

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Background and Aims: Inhibitor development in subjects with non-severe hemophilia A (NSHA) is an important issue, since it can cause a dramatic change in clinical phenotype, as the inhibitor frequently cross-reacts with the patient's endogenous FVIII, reducing its plasma level below 1 U/dL. As a result, most of these patients experience spontaneous bleeding, the treatment of which can be challenging. Bleeding may be treated with desmopressin, high doses of FVIII concentrate or FVIII bypassing agents. It is also unclear whether ITI, immune suppression, or a combination of both should be used to eradicate inhibitor in NSHA. Inhibitor occurs in about 10% of NSHA patients and the risk increases with increasing exposure days to FVIII concentrate. Specific F8 missense mutations predispose to inhibitor development, as surgical interventions, and an intensive treatment with FVIII concentrate. The aim of this study is to review the risk factors and outcome of patients with NSHA and inhibitor followed at our Centre.
Methods: In 11 subjects with NSHA and inhibitor the following data were retrospectively collected: FVIII:C levels, F8 mutation, exposure days (ED) to FVIII concentrate, other environmental risk factors for inhibitor development, clinical phenotype after inhibitor onset, lowest FVIII:C, highest inhibitor, and inhibitor outcome.
Results: Table 1.
Conclusions: In our case studies the F8 mutation (p.Arg2169His, mostly, 4 out of 7 subjects), an intensive treatment with FVIII concentrate, often due to surgery, are confirmed as important risk factors for inhibitor development in NSHA subjects. Many inhibitors disappear over time, even when continuing FVIII concentrate,

and a short successful ITI was carried out only in one case. To date, avoidance of treatment with FVIII concentrates by using desmopressin, where possible, is the single most effective way to prevent inhibitor development in NSHA patients.

Table 1.

CO052

USE OF ULTRASOUND (US) FOR JOINT EVALUATION IN HEMOPHILIA: THE MONTREAL STUDY

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Background: For hemophilic patients, optimization of joint outcomes is still an important unmet need. Traditionally, most symptoms are ascribed to joint bleeding and addressed mainly by optimizing prophylaxis. Recently, a new emphasis is on early detection and treatment of arthropathy beyond improving treatment strategies. There is rising awareness that detection and management of asymptomatic findings are essential. For this purpose, the HEAD US (Hemophilia Early Arthropathy Detection) protocol was designed, in order to detect blood effusion and joint damage before clinical manifestations. The aim of this study is to investigate use of US monitoring in evaluating arthropathy in severe hemophilia A (HA) and B (HB) patients and to find any correlation between US score and HJHS (hemophilia joint health score), ABR (annualized bleeding rate) and NRS (Numeric pain Rating Scale) evaluated at baseline, after 6 months (T1) and 12 months (T2) of regular prophylaxis.

Methods: Adult severe hemophilia A/B patients were included. At each visit articular function was evaluated with HJHS and US (HEAD US score). Joint pain (NRS), trough level, target joints and prophylaxis efficacy whit ABR were monitored.

Results: We evaluated 32 patients. Median age was 39 years old (IQR1-3 33-55,5), 7 patients had HB and had 25 had HA. Median trough level was 2.00 (IQR1-3 1.00-3.00) for HA and 10.00 (IQR1-3 10.0-11.00) for HB. Median target joints value was 2, without differences between HA and HB. Median HEAD US, NRS, HJHS and ABR at baseline, at T1 and T2 are shown in Table 1. As reported, no significant differences were found within the three timepoints and within type of hemophilia. A univariate correlation analysis was performed and no significant correlations within variables was found.

Conclusions: The exact frequency of performing US in HA and HB patients is not defined yet. Our analysis suggests that a every 6 months evaluation after baseline may be too early to detect significant intraarticular changes in patients treated with replacement therapy prophylaxis, regardless the trough level. No correlation between HEAD US score and the others parameters evaluated over time was found. These results are to be confirmed in longer follow up studies.

Table 1.

	ALL N=32	HA N=25	HB N=7	p.overall
Trough	3.00 [2.00;5.25]	2.00 [1.00;3.00]	10.0 [10.0;11.0]	<0.001
n° target joint	2.00 [2.00;3.00]	2.00 [2.00;3.00]	2.00 [1.50;3.00]	0.700
HEAD US T0	8.00 [6.00;19.2]	8.00 [6.00;20.0]	13.0 [4.00;15.5]	0.537
HEAD US T1	9.50 [6.00;18.0]	9.00 [6.00;18.0]	13.0 [3.50;15.5]	0.615
HEAD US T2	10.0 [6.00;17.0]	11.0 [6.75;17.0]	7.00 [3.50;13.5]	0.236
NRS T0	2.00 [0.00;4.25]	2.00 [0.00;3.00]	3.00 [1.00;5.00]	0.437
NRS T1	2.00 [0.00;4.00]	2.00 [0.00;3.00]	4.00 [0.50;4.00]	0.385
NRS T2	2.00 [0.00;4.00]	2.00 [0.00;3.25]	3.00 [0.00;5.50]	0.576
HJHS T0	9.50 [5.75;14.5]	10.0 [6.00;16.0]	9.00 [3.00;13.0]	0.522
HJHS T1	11.0 [5.00;17.2]	10.0 [5.00;17.0]	15.0 [3.00;20.0]	0.982
HJHS T2	9.00 [6.00;19.5]	9.00 [7.50;18.8]	10.0 [3.00;22.0]	0.831
ABR T0	1.00 [0.00;2.00]	1.00 [0.00;2.00]	1.00 [0.00;4.00]	0.592
ABR T1	0.00 [0.00;1.00]	0.00 [0.00;1.00]	1.00 [0.00;2.50]	0.161
ABR T2	0.00 [0.00;1.00]	0.00 [0.00;1.25]	0.00 [0.00;1.00]	0.957
D.HEADUS	0.00 [-1.50;1.00]	0.00 [-1.00;1.25]	-1.00 [-4.00;0.00]	0.224
D.NRS	0.00 [-1.00;0.00]	0.00 [-1.00;0.00]	0.00 [0.00;0.00]	0.721
D.HJHS	0.00 [-1.00;2.00]	0.00 [-1.25;2.25]	0.00 [0.00;1.50]	0.416
D.ABR	0.00 [0.00;0.50]	0.00 [0.00;1.00]	0.00 [0.00;0.00]	0.319

CO053

12 MONTHS JOINT HEALTH EVALUATION IN HEMOPHILIA A PATIENTS TREATED WITH EMICIZUMAB: A SINGLE CENTRE EXPERIENCE

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Background and Aims: Severe hemophilia patients commonly experience regular bleeding into joints, which may result in joint damage and degenerative arthropathy. Emicizumab has previously demonstrated efficacy in reducing the occurrence of joint bleeds and target joints, along with having a favorable safety profile; however, data on long-term effects on joint health are lacking. The aim of this study is to evaluate joint health in adult severe hemophilia A patients treated with Emicizumab through US HEAD US score (Hemophilia Early Arthropathy Detection with Ultrasound), HJHS (Hemophilia Joint Health Score), ABR (Annualized Bleeding Rate) and NRS (Numeric pain Rating Scale) evaluated at baseline, after 6 months (T1) and after 12 months (T2) of regular Emicizumab prophylaxis.
Methods: Adult severe hemophilia A patients treated with Emicizumab were included. FVIII inhibitors patients were excluded. At each visit (baseline, after 6 months and after 12 months) articular function was evaluated with HJHS and HEAD US score. Joint pain (NRS), through level and prophylaxis efficacy whit ABR were monitored, as well as target joints.
Results: We evaluated 9 patients. Median age was 24 years old (IQR1-3 22-56), median target joints value was 2 (IQR1-3 2.00-6.00). ABR was 0 for all patients at each timepoint. Median HEAD US, NRS and HJHS at baseline, at T1 and at T2 are shown in Table 1. As reported, no significant differences were found within the 3 timepoints. A univariate correlation analysis was performed and no significant correlations within variables was found; furthermore, no significant variations during observation period was found.

Table 1.

VARIABLES	T0			T1			T2			FRIEDMAN TEST P.VALUE
	Median	q1	q3	Median	q1	q3	Median	q1	q3	
HEADUS	9.00	3.00	15.00	9.00	6.00	19.00	5.00	2.00	17.00	0.607
NRS	1.00	0.00	1.00	1.50	0.00	3.00	2.00	0.00	4.00	0.223
HJHS	6.00	0.00	15.00	9.00	2.50	23.00	12.00	0.00	13.00	0.497

Conclusions: Emicizumab has demonstrated safety and efficacy in prevent bleeding, but data regarding evaluation of long-term joint health are still lacking. Despite reduced sample size, our analysis suggests that a 12 months treatment evaluation no significant differences in HEAD US score, HJHS and NRS were found. These data are in accordance with a good protection on articular bleeding (especially regarding microbleeds that are responsible of arthropathy progression), but 12 months observation may be too early to detect significant intrarticular changes. Longer follow up is needed to confirm this preliminary data.

CO054
THE BURDEN OF AGEING IN HAEMOPHILIA: A 5-YEAR ANALYSIS OF COMORBIDITIES AND COMEDICATION IN A COHORT OF ADULT/ELDERLY PATIENTS

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Background and Aims: The increase of life expectancy in persons with haemophilia (PWH) over the last decades unveiled new challenges in the disease management, due to comorbidities and polypharmacy typical of older age. Few data are currently available about the prevalence of comorbidities and comedication and the healthcare burden of ageing PWH. We analysed these issues in a cohort of adult/elderly PWH.
Methods: Five-year (2019-2023) clinical records of PWH (A and B, any severity) aged >40 yrs (in 2019) followed at a comprehensive care haemophilia center (HC, Parma, Italy) were retrospectively reviewed. Data about comorbidities and comedication s (type and number) were collected, along with number of outpatient visits at HC, specialist consultancies and diagnostic/instrumental investigations, highlighting those performed for comorbidities, other than orthopaedic and infectious disease (NOID) issues.
Results: Eighty-one patients (33% of PWH followed at the HC) were evaluated (haemophilia A/B 70/11; severe 18). Age range (in 2023) was 45-89 yrs (45-49 yrs: 12; 50-59 yrs: 38; 60-69 yrs: 19; >70 yrs: 12). Overall, 71 (87%) patients reported at least 1 comorbidity and 45 (55%) ≥3 (median 3, range 0-9) comorbidities, the prevalence progressively increasing in older age categories (in PWH aged >60 yrs: 96% and 83%, ≥1 and ≥3 comorbidities, respectively). No significant difference was found according to type and severity of haemophilia. Hypertension was the most frequent condition (45%), followed by gastrointestinal diseases (34%), cardiovascular diseases (30%), dyslipidemia (25%), diabetes mellitus (15%) and kidney diseases (10%). Concomitant medications (range 1-12) were used by 57 PWH (70%), 32 (39%) reporting intake of ≥3 drugs. Again, PWH aged >60 yrs showed higher figures (≥1 93%, ≥3 64%). Consistent with comorbidities, the most used comedications were anti-hypertensive drugs (47%), proton-pump inhibitors (21%) and statins (18%). Benzodiazepine or other neuroleptic use was reported by 14% of PWH, while 9% were on antithrombotic treatment (n=7, 6 aspirin, 1 warfarin). We recorded 581 accesses to HC/healthcare facilities due to NOID (27% of total accesses, mean±1SD 7.17±3.45) with higher impact in severe *vs* non-severe PWH (9.05±3.4 *vs* 6.63±3.43, p<0.1), in older patients (>70 *vs* 40-69 yrs; 3.77±3.79 *vs* 2.17±3.33, p<0.01) and in severe HB *vs.* HA, only concerning specialist consultancies (9.33±4.1 *vs* 4.07±3.23, p<0.05). Comorbidities were responsible for 9% of HC visits, increasing to 16% in PWH >70 yrs. About 37% of specialist consultancies and 61% of diagnostic investiga-

tions were due to NOID-related issues, again with higher rates in older patients (42% and 74% in >70 yrs).
Conclusions: Management of adult/elderly PWH is increasingly addressing the comorbidity and comedication issues, in parallel with ageing. More than 80% of PWH aged >40 yrs suffer from at least 1 comorbidity and 70% report comedication intake, with higher rates and impact in older patients. In parallel, the healthcare burden (likely underestimated due to pandemic years included in our analysis), is relevant, being responsible for almost 30% of healthcare accesses in our cohort and increasing with ageing. These aspects should be considered in healthcare planning and in further personalization of comprehensive care for PWH.

CO055

PREDISPOSING CONDITIONS AND DRUGS TO CAPLACIZUMAB-RELATED BLEEDING EPISODES IN PATIENTS WITH ACUTE IMMUNE-MEDIATED TTP: REAL-WORLD DATA FROM THE MILAN CENTER

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Background and Aims: The humanized bivalent nanobody caplacizumab has changed the therapeutic paradigm in acute immune-mediated thrombotic thrombocytopenic purpura (iTTP). However, real-world data on its safety are still limited, especially in patients with concomitant bleeding risk factors. This study aims to estimate the incidence of caplacizumab-related bleeding episodes and identify the main risk factors associated with these episodes.
Methods: In this cross-sectional study, we included outpatients followed at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center (Milan, Italy) who received caplacizumab for an acute iTTP episode occurred between September 2018 and October 2023. Data on bleeding episodes occurred during caplacizumab treatment were retrospectively collected, alongside patient- and episode-related features, clinical conditions and drugs that increase bleeding risk.
Results: Out of 61 acute iTTP episodes, 8/61 (13%) were complicated with caplacizumab-related bleeds, including 4 major bleeds, 2 clinically-relevant non major bleeds (CRNMBs), and 2 minor bleeds. Predominantly, these bleeding events occurred in patients with predisposing bleeding conditions. In particular, the four major bleeds, all requiring caplacizumab stop, included: i) an episode of melena in a patient with pyloric ulcer, leading to severe anemia, requiring Emergency Department (ED) admission and red blood cell transfusion (2 units); ii) an episode of hemoptysis leading to severe anemia requiring red blood cell transfusion, intravenous factor VIII/VWF concentrate and emergency transcatheter arterial embolization, occurred in a patient with concomitant acute SARS-CoV2 pneumonia, complicated with disseminated intravascular coagulation and multiorgan failure syndrome, and daily treated with aspirin and prophylactic enoxaparin; iii) a right periorbital hemorrhagic suffusion with loss of vision; iv) a vaginal bleed leading to severe anemia requiring red blood cell transfusion (6 units), in a patient undergoing a Caesarean section 1 month before. The two CRNMBs included a severe epistaxis requiring ED admission and nasal hemostatic swab in a patient treated with aspirin, and a trauma-related oral bleed, requiring hemostatic swab and packing and the suspension of only one dose of caplacizumab. The two minor bleeds (hematuria; mild bilateral epistaxis with mild rectal bleed) did not require caplacizumab stop and both occurred in patients with hypertension and treated on aspirin or heparin. Patients with caplacizumab-related bleeding chronically used a significantly higher median number of drugs (p=0.03), with increased daily use of antiplatelet and anticoagulant drugs [OR: 5.6 (1.4-21.8, p=0.04)]. No difference in the severity of TTP episodes was found between the two groups (Table 1). Notably, bleeding events occurred 3 to 27 days after caplacizumab start, generally after platelet count normalization.
Conclusions: Although further studies with larger sample size are needed, our findings suggest that the risk of bleeding related to caplacizumab is mostly secondary to the concomitant use of antiplatelet agents and anticoagulants. A careful revision of the therapeutic indications of these concomitant drugs and the related risk-benefit balance is recommended during caplacizumab treatment.

Table 1.

Patient- and episode-related features in iTTP episodes with and without caplacizumab-related bleeds.

	with caplacizumab-related bleeds n = 8	without caplacizumab-related bleeds n = 53	Difference of medians/proportions (95% CI)
1st iTTP episode, n (%)	8 (97.5)	42 (60.4)	-12 (-30; 11)
age, years, median (IQR)	53 (46.5-56.2)	51 (40-58)	1 (-9; 9)
female, n (%)	7 (87.5)	38 (71.7)	9 (-14; 25)
number of daily (no TTP-related) chronic drugs, median (IQR)	2.5 (1.8-4.1)	1 (0-2)	1 (0-2)
concomitant use of antiplatelet agents or anticoagulants, n (%)	4 (50)	8 (15.1)	25 (6; 57)
hypertension, n (%)	4 (50)	14 (26.4)	13 (-7; 40)
platelet count at onset, 10^9/L, median (IQR)	8 (5-37)	13 (8-21)	-2 (-12; 16)
troponin at onset, higher than ULN, n (%)*	3 (60)	10 (35)	2.5 (-26; 28)
hemorrhagic signs/symptoms at onset, n (%)	2 (25)	23 (43.4)	-8.7 (-40; 9.4)
neurological signs/symptoms at onset, n (%)	6 (75)	39 (73.6)	0.8 (-27; 18)
length of caplacizumab treatment, median (IQR)	26 (17-42)	33 (29-46)	-7 (-27; 13)
rituximab, n (%)	5 (62.5)	28 (52.8)	4.4 (-16; 24)
refractoriness, n (%)	0	1 (1.8)	Not applicable
number of TPE to achieve clinical response, median (IQR)	5.5 (4.8-11.3)	6 (5-9)	-1 (-3; 3)

*available in 5 (with caplacizumab-related bleeds) and 33 (without caplacizumab-related bleeds).
CI: confidence interval; IQR: interquartile range; TPE: therapeutic plasma exchange; TTP: thrombotic thrombocytopenic purpura; ULN: upper limit of normal range.
Neurological signs/symptoms: headache, ischemic stroke, transient ischemic attack, epileptic seizures, coma, personality disorders, focal neurological signs.
Hemorrhagic signs/symptoms: skin bleeding (purpura, bruising), mucosal bleeds (including epistaxis), hematuria, meno-metrorrhagia, gastrointestinal hemorrhages.

CO056

RELATIONSHIP BETWEEN VWF ACTIVITY AND ADAMTS-13 IN THE FOLLOW-UP OF IMMUNE THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background and Aims: Immune thrombotic thrombocytopenic purpura (iTTP) is associated with ADAMTS-13 autoantibodies and recurs in approximately 40% of cases. It is known that patients with ADAMTS-13 below 10% (or 1 UI/dl) are more exposed to relapses. In the disease pathophysiology, a key player is the von Willebrand factor (VWF), that is cleaved by ADAMTS-13 in the A2 domain. Our hypothesis is that circulating VWF levels may fluctuate especially in patients prone to exacerbations or relapse. Therefore, we prospectively measured ADAMTS-13 and VWF in a cohort of iTTP patients referred to our Unit after a first acute event.
Methods: This single-centre cohort study consecutively enrolled iTTP patients referred to our Thrombosis and Haemostasis Unit after first event. We prospectively followed our patients and collected at each follow up clinical data, blood count, ADAMTS-13 plasma levels, vWF antigen and ristocetin cofactor activity (RCo). Clinical and laboratory data related to the first event, exacerbations and relapses and therapeutic strategies were collected. ADAMTS-13 activity and functional VWF were measured using commercial ELISA and ristocetin cofactor activity methods, respectively. Exacerbation and relapse were defined as a platelet count decreases (<150 x 109/L) within 30 d of stopping plasma-exchange and after a complete clinical remission, respectively. The study was approved by the local Ethics Committee and a patient informed consent was obtained.
Results: Overall, we enrolled 16 patients (12 women, 75%) with median age 45.0 years (IQR: 10.0). Follow-up lasted 5.0 years (median 4.5, IQR: 4.0 yrs), with a mean of 6,2 visits/year. Median age at the first diagnosis was 42.0 (IQR: 10.0). At the first iTTP episode, all the patients were treated by plasma-exchange and steroids, whereas Rituximab (375 mg/m2/week-4 doses) was used in 13 out of 16 (81.2%). Three patients (18.7%) were treated with standard regimen of Caplacizumab. During the follow-up, four patients (28%, 3 women) relapsed: all were treated with Rituximab (375 mg/m2/week-4 doses), none with Caplacizumab. The relapsing rate was 5/100 patients-year. During the follow-up, the observed median platelet count was 237 x 109/L (IQR: 110) and IgG anti-ADAMTS-13 titres 6.0 U/ml (IQR: 10) (negative values <12.0). We found a significant inverse relationship between ADAMTS-13 activity and VWFRCo (Figure 1a, linear regression: p=0.005) during the entire period of follow-up. Figure 1b illustrates trends in ADAMTS-13 and VWFRCo (Figure 1b) in a patient prone to recurrent pulmonary infections with multiple TTP relapses: the graph shows inverse variations in ADAMTS-13 activity and VWFRCo at the relapsing episodes and in the relapse-free interval period. Figure 1c shows ADAMTS-13 and VWFRCo variations in one woman with an exacerbation and a relapse taking habitually nonsteroidal anti-inflammatory drugs (Figure 1c). This relationship was not observed in two patients who were treated with Caplacizumab during relapses. No significant relationship was observed with VWF Antigen.
Conclusions: These preliminary data suggest that VWF testing during iTTP follow-up can be a good marker of exacerbation or relapses. Larger studies are warranted.

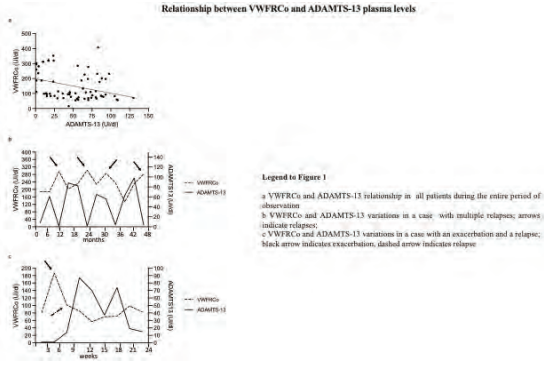

Figure 1.

CO057

IN VIVO AND *IN VITRO* MODULATION OF PLATELET BALANCE BETWEEN PRODUCTION AND DESTRUCTION AFTER TOFACITINIB TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background and Aims: Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by inflammation and joint destruction. Atherothrombosis is a common comorbidity associated with arthritis and inflammation and represents the cornerstone of the raised cardiovascular (CV) risk in these patients. Tofacitinib (TOF) is an oral JAK inhibitor for the treatment of RA. Platelets are strongly activated by inflammatory triggers, and are able, in turn, to amplify inflammation and endothelial dysfunction. The effects of JAK inhibitors on platelets or their progenitors, megakaryocytes (MKs), if any, are partially uncharacterized. JAK-2 modulation may affect thrombopoiesis. Our aims were to assess, in patients with RA, the effects of 6-month TOF treatment on *in vivo* and *in vitro* modulation of the balance between platelet production and destruction.
Methods: Twenty-four patients with a diagnosis of RA, who were intolerant or had an inadequate response to at least one csDMARD drug, were enrolled in a prospective 6-month, observational study. We enrolled also healthy subjects. CD34+ cells from healthy subjects were cultured with 10 ng/mL Thrombopoietin in the presence of

0, 0.1, 0.3, 1 uM TOF to assess influence on MK differentiation and platelet formation capacity.
Results: TOF was shown to influence circulating levels of thrombopoietin, the primary regulator of platelet production through the JAK-STAT pathway, that were stably reduced (T0 *vs* T3, p= 0.011; T0 *vs* T6, p= 0.002) (Figure 1, panel A) already after three months of TOF. Conversely, we showed an increase in circulating GC (T0 *vs.* T3, p=0.181; T3 *vs.* T6, p<0.001; T0 *vs.* T6, p<0.001) (Figure 1, panel B) the extramembranous portion of GPIbα, index of platelet destruction, and in GCI (T3 *vs.* T6, p <0.001; T0 *vs.* T6, p <0.001) levels, after three and six months of Tofacitinib treatment (Figure 1, panel C). We observed higher levels of GPIbα (T0 *vs.* T6, p=0.048) (Figure 1, panel D, E) and increased levels of ADAM17, the mediator of GPIbα shedding from platelets (T3 *vs.* T6, p=0.039) (Figure 1, panel D, F). TOF treatment, *in vitro*, did not influence MK differentiation, survival, ploidy and diameters, or surface marker expression. Though, we showed a dose-dependent decrease in cell proliferation at high drug concentrations (Figure 1, panel H), paralleled by the inhibition of proplatelet formation (Figure 1, panel G-I).
Conclusions: Tofacitinib may affect JAK/STAT-dependent TPO liver synthesis and MK proliferation. Activation of ADAM-17 with increased GP1balpha ectodomain shedding, resulting in higher GC circulating concentrations, may be due to the TOF-dependent reduction of TNF signature, which have been shown to reduce ADAM17 shedding activity. Further insights are certainly needed to understand how TOF can affect platelet production and what mechanisms are responsible, and whether this translates into meaningful cardiovascular benefit of JAK inhibitors.

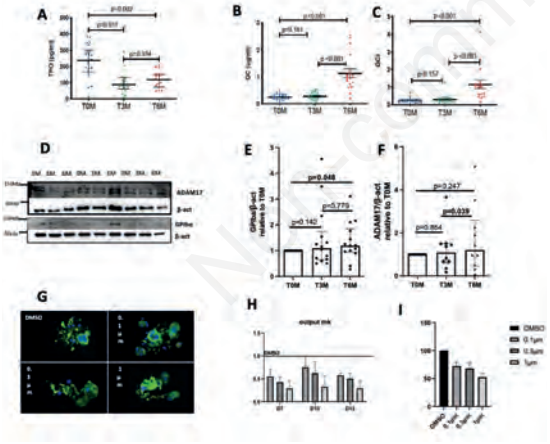

Figure 1.

CO058

A DIAGNOSTIC APPROACH TO IMPROVE THE IDENTIFICATION OF INHERITED THROMBOCYTOPENIAS IN A COHORT OF ADULT PATIENTS

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Background and Aims: Inherited thrombocytopenias (ITs) represent a heterogeneous group of genetically determined disorders of platelet production or function. Currently, ITs include 45 known disorders caused by mutations in 40 genes, characterized by different degrees of severity related to a broad spectrum of hemorrhagic manifestations and additional comorbidities. Despite the advances in medical science, they often remain underdiagnosed or wrongly framed as immune forms, leading to inadequate clinical, diagnostic and therapeutic management. The introduction of multigenic sequencing techniques (NGS), may rapidly expand knowledge of these nosological entities and identify new gene loci responsible for their occurrence.
Methods: Since October 2021, all subjects, among those with thrombocytopenia of uncertain significance afferenting to First Medical Clinic of University Hospital of Padua were enrolled based on suspicious criteria such as thrombocytopenia with chronic course, family history, failure to respond to first-line therapy for ITP; patients with a previous normal platelet count, acute worsening of thrombocytopenia or acute hemorrhagic diathesis and all secondary thrombocytopenias were excluded. The diagnostic work-up first included the evaluation of platelet diameter and morphology on peripheral blood smear by May-Grunwald/Giemsa staining, the assessment of antigen expression on platelet surface through cytofluorimetric techniques, and platelet aggregation tests according to Born. A preliminary search for mutations in MYH9, in 5'UTR of ANKRD26 and genes coding for the GPIBa/GPIBb/GPIX/GPV complex was conducted by PCR amplification and sequencing using the Sanger's method. In cases in which first level genetic investigations did not lead to the identification of the causative mutation, the genetic study was expanded by NGS.
Results: 152 patients belonging to 64 families are currently being enrolled. Sequencing by Sanger method was conducted in 133 and led to the identification of the causative mutation in 72 (47.3%) subjects. Among these, 36 (23.6%) had mutations responsible for Bernard Soulier Syndrome (BSS), and the most frequent variant was Ala156Val (6.5%). In 26 (17.1%) patients, variants associated with MYH9-related disease were detected. In 10 (6.5%) subjects a mutation in the 5'UTR region of the ANKRD26 was found. NGS has been conducted so far in 13 patients resulting in wild type or VUS carriers at Sanger method. In one patient the variant NM_022437.3:c490C>T, p.(Arg164Ter) in homozygosity in the ABCG8 gene associated with Sitosterolemia 1 with autosomal recessive transmission was detected. In the other cases (23.6%) a variant of uncertain significance (VUS) was found.
Conclusions: Our proposed diagnostic work-up includes firstly the identification of clinical-anamnestic data, that should induce suspicion of a IT. The study of platelet morphology, immunophenotype and platelet aggregation, can reveal alterations that support the genetic hypothesis. The combination of these data could help to

select subjects for in-depth genetic study, in which NGS could play a role in identification of additional unknown mutations. According to literature, in our cohort the most common forms of ITs appear to be monoallelic BSS, MYH9-RD followed by ANKRD26. A mutation associated in the literature with Sitosterolemia 1 was found in one patient. Further investigations will be needed to clarify the pathogenic significance of VUS.

CO059

ASSESSING THE SAFETY OF PLATELET TRANSFUSIONS IN PATIENTS WITH THROMBOTIC THROMBOCYTOPENIC PURPURA: PRELIMINARY RESULTS FROM A SYSTEMATIC REVIEW OF PUBLISHED STUDIES

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Background and Aims: Thrombotic thrombocytopenic purpura (TTP) is a critical thrombotic microangiopathy characterized by a severe deficiency of the ADAMTS13 enzyme. This condition is potentially life-threatening and often presents with both thrombotic and bleeding complications. In clinical practice, platelet (PLT) transfusions are frequently administered to manage bleeding symptoms or prepare for invasive procedures like surgery or central venous catheter placement, essential for plasma exchange, the cornerstone of TTP emergency treatment. Nevertheless, the safety of PLT transfusions remains controversial, with some studies suggesting an association with increased mortality. To clarify these concerns, we conducted a systematic review focusing on the safety of PLT transfusions in this patient population.
Methods: Medline and Embase were searched independently by two researchers (E.T. and C.B.) since inception until January 30, 2024. We included peer-reviewed studies in English providing data on the primary safety outcome (all-cause death) in patients with TTP and documented PLT transfusion status. We excluded studies if the diagnosis of TTP was not confirmed by laboratory documentation of ADAMTS13 activity below 10% and if fewer than 5 TTP patients were described, to minimize selection bias. Secondary safety outcomes assessed included the rates of acute myocardial infarction (AMI), coma, seizure and cerebrovascular accidents (CVA). Where available, patient-specific data such as age, treatment courses and platelet count nadirs were extracted to gauge disease severity. Data are presented as proportions with 95% confidence intervals (CI) calculated with the exact method.
Results: We included 6 studies, describing 270 transfused and 546 non-transfused TTP patients. The primary outcome event occurred in 18% of the transfused subjects (95% CI, 14-23) and in 13% of the non-transfused subjects (95% CI, 10-16) (p=0.05) (Table 1). The time interval between the last PLT transfusion and death was known for 74 subjects: only 4 deaths occurred within 24 hours of the latest PLT transfusion (5%, 95% CI 1-13). The rates of AMI and CVA were comparable between transfused [3% (95% CI, 1-6) and 12% (95% CI, 8-17)] and non-transfused subjects [4% (95% CI, 0.5-13) and 11% (95% CI, 4-23)], with non-significantly higher rates of coma in transfused subjects (transfused: 11%, 95% CI 7-17; non-transfused: 5%, 95% CI 0-24; p=0.71) and of seizure in non-transfused subjects (transfused: 7%, 95% CI 4-11; non-transfused: 11%, 95% CI 4-23; p=0.42) (Table 1). We were unable to retrieve enough non-aggregate clinical data to attempt to compare disease severity between eligible transfused and non-transfused TTP patients (not shown).
Conclusions: The preliminary results of this systematic review suggest a slightly higher, but non-statistically significant, rate of all-cause death in TTP patients who received PLT transfusions compared to those who did not. This could suggest potential harm from transfusions or reflect a greater baseline disease severity in those requiring this intervention. Only a small fraction of transfused patients died within 24 hours of their latest PLT transfusion. This study is limited by the high heterogeneity and low quality of included studies (mainly retrospective case series or cohort studies with heterogeneous endpoints). To conclusively determine the safety of PLT transfusions in TTP, further high quality prospective studies are essential.

Table 1.

Primary and secondary outcome events in patients with thrombotic thrombocytopenic purpura who received (n=270) and did not receive (n=546) at least one platelet transfusion

	Primary outcome event					
	Transfused patients (N=270)		Non-transfused patients (N=546)			
	n/N (%)	95% CI	n/N (%)	95% CI	Chi square	P value
All-cause death	49/270 (18)	14-23	71/546 (13)	10-16	3.812	0.0509
	Secondary outcome events					
	Transfused patients (N=270)		Non-transfused patients (N=546)			
	n/N (%)	95% CI	n/N (%)	95% CI	Chi square	P value
AMI	5/206 (3)	1-5	2/53 (4)	0.5-13	0.104[2]	0.7466
CVA	24/206 (12)	8-17	6/53 (11)	4-23	0.004[2]	0.9467
Coma	21/183 (11)	7-17	1/21 (5)	0-24		0.7074[3]
Seizure	14/206 (7)	4-11	6/53 (11)	4-23	0.659[2]	0.4168

Abbreviations: CI, Confidence interval; AMI, acute myocardial infarction; CVE, cerebrovascular accidents. Comparisons between categorical variables were performed with the Chi square test, unless otherwise indicated. [2]Calculated with Chi square test with Yates correction; [3]Calculated with Fisher's exact test.

CO060

MEGAKARYOCYTES DERIVED FROM INDUCED PLURIPOTENT STEM CELLS OF PARAHAEMOPHILIA PATIENTS TO STUDY RESTORATION OF PLATELET FACTOR V

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Background and Aims: Congenital factor V (FV) deficiency (parahaemophilia) is a rare autosomal recessive bleeding disorder. FV is present both in plasma (80%) and in platelet a-granules (20%). Platelet FV is stored in

a partially activated form which makes it readily available. Megakaryocytes (MKs) from parahaemophilia patients represents a powerful tool to characterize platelet FV and to develop new therapies to compensate for genetic defects. Induced pluripotent stem cells (iPSCs) owing to the unlimited proliferative ability and multi-directional cell differentiation have become the ideal model of cells to study different cellular aspects. One of the key advantages of using iPSCs is the ability to create a disease-specific cell line, thus in the case of parahaemophilia patients, the iPSCs generated carry the same genetic mutations found in the patient providing an invaluable tool for studying the molecular mechanisms underlying the pathology. Through the comparison with healthy iPSC-derived cells, it is possible to identify specific changes associated with the disease. This knowledge can then be used to develop targeted therapies that specifically against the genetic defects in individual patients. Furthermore, this personalized *in vitro* approach is very promising for verifying which is the best therapy choice. The focus of our studies is to generate MKs through the generation of iPSCs starting from the patient peripheral blood mononuclear cells (PBMC).

Methods: The parahaemophilia patient's PBMCs were reprogrammed for iPSCs. In order to test the pluripotency state, the pluripotency markers OCT4, Nanog, SOX2, hTert, Rex1 and Dmn3b were analyzed by RT-PCR upon cell RNA extraction. In addition, expression of pluripotency proteins OCT4, nanog, SSEA3, SSEA4 and TRA1-60 were evaluated by immunofluorescence. iPSCs obtained from healthy and parahaemophilia subjects were differentiated into the MKs lineage. iPSC-MKs were analysed for the expression of CD41 and FV with the immunofluorescence technique. Finally, exogenous purified FV was added to the culture medium to evaluate the ability of iPSC-MKs to internalize FV.

Results: iPSC-MKs were capable of platelet formation *in vitro*, showing no major differences in morphology and function with as compared to blood platelets. iPSC-MKs cells were stained with CD41 to confirm that these iPSC-MKs were MKs-like cells. iPSCs-MKs from healthy subjects were positive for the expression of FV. To the contrary, iPSC-MKs from parahaemophilia patients were negative for the expression of FV. However, after the addition of purified FV to the culture medium, iPSC-MKs from parahaemophilia patients became positive after FV staining demonstrating their ability to endocytose exogenous FV. Finally, lysis of platelets derived from iPSC-MKs was performed in order to measure FV antigen levels by an ELISA assay and confirmed by Western Blot.

Conclusions: iPSC-MKs from parahaemophilia patients were unable to synthesize FV due to genetic defects but they can restore their FV content by the uptake of exogenous FV. As a result, platelets that will be produced in the following days will contain FV and they will protect against bleeding for several days. The ability to obtaining iPSCs-MKs provide evidence that this technique represents a promising cell model for elucidating platelet pathophysiology, for drug screening tests and for developing a gene therapy to correct the genetic defects. The ability of iPSC-MKs to uptake purified FV can be considered a useful rescue mechanism that may have important clinical implications in the management of parahaemophilia patients.

CO061

VENOUS THROMBOEMBOLISM PROPHYLAXIS AFTER SURGERY FOR HIP FRACTURE: A SURVEY OF PHYSICIAN PRACTICES AND PREFERENCES FROM THE HIPSTER STUDY GROUP

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Background and Funding: Guidelines on venous thromboembolism (VTE) prevention after hip fracture surgery suggest using low-molecular-weight heparin (LMWH) but based on very-low-certainty evidence. There is emerging evidence that direct oral anticoagulants (DOACs) or acetylsalicylic acid (ASA) might be safe and effective alternatives. We received funding from the Canadian Venous Thromboembolism Research Network to conduct a pilot randomized controlled trial (RCT) that will address this question.

Aims: To survey physician practice regarding VTE prophylaxis for people undergoing hip fracture surgery and preferences regarding interventions they would consider acceptable for an RCT.

Methods: We recruited a convenience sample of physicians potentially involved in the prescription of VTE prophylaxis after hip fracture surgery. We distributed the survey (August-December 2023) by email through professional organizations (including SISET and ISTH) and social media. Participants providing informed consent answered 14 questions on demographics, their current practices for VTE prevention after hip fracture surgery, the need for an RCT on this topic, and acceptable interventions.

Results: 204 physicians from 28 countries completed the survey, with 175 (86%) being responsible for prescribing postoperative VTE prophylaxis. 172 (84%) indicated that an RCT is needed. 67% of the respondants were in the age range between 40 and 69 years, 42% were woman. 120 (59%) physicians reported using LMWH, and ≥25% rivaroxaban/apixaban alone or after a short course of LMWH. Regarding preferences for RCT interventions, LMWH and LMWH followed by rivaroxaban/apixaban were ranked highest. 140 (69%) participants would not be comfortable if the RCT interventions included ASA alone, and >40% would be uncomfortable with ASA following a short course of anticoagulant. Among orthope-

dic surgeons, the percentage uncomfortable with ASA alone was 39%.
Conclusions: LMWH was the standard of care for most of our respondents. If they were to participate in an RCT, they would prefer a trial comparing LMWH with LMWH followed by rivaroxaban/apixaban.

CO062

THE RISK OF CEREBRAL VEIN THROMBOSIS ASSOCIATED WITH DIFFERENT TYPES OF ORAL CONTRACEPTIVES: A CASE-CONTROL STUDY

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Background and Aims: Cerebral vein thrombosis (CVT) is a rare manifestation of thrombosis. CVT typically affects young adults and is more common in women than in men because of sex-specific risk factors such as oral contraceptive (OC) use and pregnancy/puerperium. So far, data on the risk stratification of CVT according to different types of OC are scarce. The aim of this case-control study was to assess the risk of CVT according to different types of OC and the joint effect with thrombophilia abnormalities and family history.
Methods: The study included women of childbearing age after an episode of CVT and healthy women (friends or acquaintances of patients) referred to our Center from 1992 to 2019 for a thrombophilia work-up. Odds ratios (OR) with their relative 95% confidence intervals (CI) were calculated to quantify the association between different types of OC, thrombophilia and family history, and the risk of CVT.
Results: The study was conducted on 206 cases (157 OC users and 49 non-users), median age 33 years (26-41) and 869 controls (198 OC users and 671 non-users), median age 34 years (27-41). Obesity was represented in 21 cases (10.3%) and 37 controls (4.3%). A positive family history for VTE was reported in 115 cases (57%) and 201 controls (23%). Thrombophilia abnormalities, including factor V Leiden, prothrombin G20210A, antithrombin, protein S and protein C deficiencies, and antiphospholipid antibodies, were present in 35% cases and 9.7% controls. The majority of CVT cases were provoked by OC use (85%), while 7(3%) were provoked by other risk factors. Overall, the risk of CVT in OC users was 10-fold higher than in non-users (OR 10.9; 95%CI:7.6-15.6). The risk estimates increased with the progestin generation, with the highest figures observed for the fourth-generation pills (OR 28.3, 95%CI:14.6- 54.9). Estrogen doses >30 µg were associated with the highest risk (OR 12.4; 95%CI:8.0-19.0), while biphasic or triphasic OCs carried a 6-fold increased risk, similar to that observed for OCs containing only progestin. Thrombophilia abnormalities were associated with a 5-fold increased risk of CVT, showing a synergistic effect with the use of OC (OR 67.8; 95%CI: 34.6-133.0). For OC users with positive family history the joint effect ranged from 25.3 (95%CI: 7.2-88.8) to 168.7 (95%CI: 36.7-775.8) according to different progestin generations (Table 1).
Conclusions: The risk of CVT in women during OC use is influenced by complex interactions between OC type and positive family history.

Table 1.

Interaction between positive family history and oral contraceptive use on the risk of CVT according to progestin generation.

OC/FAM/GEN	Controls N=861	Cases N=195	OR (95%CI)
-/-/-	506	24	Ref.
-/+/-	159	24	3.2 (1.8-5.8)
+/-/1	11	4	7.7 (2.3-25.9)
+/-/2	8	3	7.9 (2.0-31.7)
+/-/3	121	38	6.6 (3.8-11.5)
+/-/4	14	15	22.6 (9.8-52.1)
+/+/1	5	6	25.3 (7.2-88.8)
+/+/2	2	7	73.8 (14.5-374.3)
+/+/3	33	58	37.1 (20.5-67.0)
+/+/4	2	16	168.7 (36.7-775.8)

OC: oral contraceptive use; FAM: positive family history; GEN: progestin generation

CO063

VENOUS THROMBOEMBOLISM IN PATIENTS WITH HYPOALBUMINEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Aims: Hypoalbuminemia is defined by serum values <3.5 g/dl. While the risk of arterial events associated with hypoalbuminemia is well established, that of venous thromboembolism (VTE) is unclear. The objective of this systematic review and meta-analysis is to assess the VTE risk in patients with hypoalbuminemia compared to patients with normal albumin values.
Methods: MEDLINE and EMBASE were searched up to January 2024 for randomized controlled trials and observational studies. The outcome of interest was the risk of VTE in patients with hypoalbuminemia compared to patients with normal albumin values. Risk

ratios (RRs) with 95% confidence intervals (CIs) were calculated in a random-effects model. Sensitivity analysis was performed sorting patients for clinical setting *(i.e.*, medical or surgical). Heterogeneity among the included RCTs was evaluated with the Mantel–Haenszel test and I2 statistic.

Results: A total of 2,531,091 patients were included from 43 studies. One study was a post-hoc analysis of a randomized trial, 9 had a prospective and 33 a retrospective design. Eleven studies included 39,738 medical patients (29,434 outpatients and 10,304 hospitalized) while 32 studies 2,491,353 hospitalized surgical patients. Eighty percent of the studies used a cut-off value for hypoalbuminemia definition of 3.5 g/dl. Follow-up duration was 30 days in 60.5% of studies. Nine percent *versus* 3.8% of patients (7 studies) received anticoagulants. Patients with hypoalbuminemia had a higher risk of VTE than patients with normal albumin values (RR, 1.88; 95% CI, 1.66-2.13). RRs were similar in both medical (RR, 1.87; 95% CI, 1.53-2.27) and surgical patients (RR, 1.87; 95% CI, 1.61-2.16) and in patients with (RR, 1.86; 95% CI, 1.66-2.10) and without cancer (RR, 1.89; 95% CI, 1.47-2.44).

Conclusions: Patients with hypoalbuminemia have an increased risk of VTE compared to patients with normal albumin values. This risk is maintained in both medical and surgical patients and irrespective of cancer coexistence.

CO064

RISK FACTORS FOR VENOUS THROMBOEMBOLISM AFTER SURGERY FOR LUNG TRANSPLANTATION

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Background and Aims: Venous thromboembolism (VTE), *i.e.*, deep vein thrombosis (DVT) or pulmonary embolism (PE), may complicate lung transplantation, particularly DVT at the site of vascular access.

The aims of this study were: 1) to evaluate the association between patients' and donors' characteristics and the risk of VTE in the post-operative period after lung transplantation; 2) to evaluate the discriminative ability of a model containing these predictors to identify patients who are likely to develop VTE in this setting.

Methods: Consecutive patients who underwent lung transplantation from February 2020 to March 2024 were included in this study. We considered all VTE episodes (lower or upper limb DVT or PE) occurred during hospitalization after surgery. In a multivariable logistic regression model, the following risk factors for VTE were considered: age of recipient, sex, body mass index (BMI), ABO blood group, use of Extra-Corporeal Membrane Oxygenation (ECMO), *ex-vivo* lung perfusion and Oto score. Odds ratios (OR) for VTE with their 95% confidence intervals (CI) were calculated. The predictive ability of this logistic model was measured in terms of discrimination by calculating the area under the receiver operating characteristic (ROC) curve (AUC), together with its 95% CI.

Results: One hundred and one patients were included, 61 males (60%), median age (min-max) 52 years (16-69), median BMI (min-max) 23.2 Kg/m^2 (15.1-33.9). Non-O blood group was represented in 52 patients (52%) and ECMO was used in 64 patients (63%). A total of 38 VTE episodes were recorded (mostly DVT at the sites of venous access), of which 25 in the intensive care unit. The results of the logistic analysis are represented in Table 1. The risk factors mostly associated with VTE were ECMO use (OR 4.4 [95%CI: 1.5 – 12.7]) and Oto score (OR 2.7 [95%CI: 0.9 – 8-7] for >4 *vs* ≤2). The AUC of the logistic model was 0.72 (95%CI: 0.60 – 0.83).

Conclusions: ECMO use and Oto score >4 were the most important risk factors for VTE during hospitalization after lung transplantation. This predictive model showed a promising discriminative ability to identify patients who will develop VTE in the post-operative period after lung transplantation.

Table 1.

Results of the multivariable logistic regression analysis

Risk factors	no VTE (n=63)	VTE (n=38)	Odds ratio (95% CI)
ECMO use, n (%)			
no	29 (46)	8 (21)	1 (ref.)
yes	34 (54)	30 (79)	4.4 (1.5 – 12.7)
Oto score, n (%) *			
≤ 2	22 (71)	9 (27)	1 (ref.)
3 – 4	19 (68)	9 (32)	1.1 (0.3 – 3.5)
> 4	14 (25)	15 (45)	2.7 (0.9 – 8.7)
Sex, n (%)			
female	25 (40)	15 (39)	1 (ref.)
male	38 (60)	23 (61)	1.3 (0.5 – 3.8)
ABO blood group, n (%)			
O	30 (48)	19 (50)	1 (ref.)
non-O	33 (52)	19 (50)	1.2 (0.4 – 3.0)
Age (yrs), median (min, max) †	49 (16-69)	51 (18-63)	1.1 (0.8 – 1.6)
BMI (Kg/m^2), median (min, max) ¶	22 (15-34)	23 (15-33)	1.0 (0.5 – 1.8)
Ex-vivo lung perfusion, n (%)			
no	52 (83)	32 (84)	1 (ref.)
yes	11 (17)	6 (16)	0.9 (0.1 – 8.1)

VTE = venous thromboembolism; ECMO = Extra-Corporeal Membrane Oxygenation
BMI = Body Mass Index; 95% CI = 95% confidence interval; ref. = reference category
* data missing for 13 patients (5 with and 8 without VTE)
† odds ratio for every 10-year increase
¶ odds ratio for every 5-unit increase

CO065

PADUA PREDICTION SCORE AND HOSPITAL ACQUIRED PROXIMAL AND ISOLATED DISTAL DEEP VEIN THROMBOSIS

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Background and Aims: Hospital acquired deep vein thrombosis (DVT) is an important cause of morbidity and mortality. The purpose of this study was to evaluate the prevalence of lower limb proximal DVT and isolated distal DVT (IDDVT) and the relationship with the Padua Prediction score (PPS) in acutely ill hospitalized medical patients.
Methods: In a single center cross-sectional study, all inpatients from medical departments with suspected lower-extremity DVT were evaluated with whole-leg ultrasonography over a period of 183 days from 2016 to 2017.
Results: Among the 507 inpatients (age 78.0±13.3 y, females 59.2%) from medical departments, 204 (40.2%) had PPS ≥4, but only 54.4% of them underwent pharmacological thrombo-prophylaxis. Whole leg ultrasonography detected 47 proximal DVTs (9.3%) and 65 IDDVTs (12.8%). Proximal DVT prevalence was higher in patients with high PPS *vs* those with low PPS (12.7% *vs.* 7.0% p=0.029, respectively), whereas IDDVT prevalence was similar in patients with high and low PPS score (14.7% *vs.* 11.6% p=0.311, respectively). The area under the receiver operating curve (AUC) for the PPS was 0.62±0.03 for all DVTs, 0.64±0.04 for proximal DVT, 0.58±0.04 for IDDVT.
Conclusions: In hospitalized patients, IDDVT has a similar prevalence regardless of PPS risk stratification. Adherence to thrombo-prophylaxis in medical patients was still far from optimal.

CO066

IDIOPATHIC UPPER EXTREMITY DEEP VEIN THROMBOSIS: REAL WORLD DATA

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Background and Aims: Spontaneous deep vein thrombosis of the upper limbs are rare events with an incidence of 1-2 cases per 100,000 inhabitants per year, and which have so far been poorly characterized in the literature. However, they often affect patients who are on average younger than those with lower limb events and with fewer comorbidities.
Methods: We retrospectively collected information about patients with spontaneous thrombosis of the upper limbs followed by the Thrombosis Center of the AOU-Careggi. In particular, we evaluated the clinical-anamnestic characteristics of these patients, as well as the presence of thrombotic risk factors, such as thrombophilia, the use of estrogen-progestin therapy or thoracic outlet syndrome or strains/traumas preceding the event. We also compared the therapeutic regimens used, *i.e.* LWMH/VKA *versus* DOACs, in terms of efficacy and safety in the acute phase therapy of the event. Finally, we collected information about the rate of recurrence and the development of post-thrombotic syndrome during follow-up.
Results: We enrolled 92 cases with an average age of 38 years (+/- 13), with an equal male/female ratio. A third of the women were taking estrogen-progestin at the time of the event, while only in 15% of cases it was possible to identify a particularly intense effort prior to the event. Thoracic outlet syndrome was found in one third of patients, whereas only one fifth of patients had underlying thrombophilia. All events were unilateral and 12 cases were complicated by pulmonary embolism. No deaths were recorded. From the comparison between patients treated with LWMH/VKA (57) *versus* those treated with DOAC (35), no statistically significant differences emerged in efficacy and safety in terms of major or clinically relevant bleeding. The average follow-up was 49 months and in the total population only three patients developed a post-thrombotic syndrome at least moderate degree, measured on the basis of clinical criteria and the impact on the patient's life. Totally, there were 14 relapses following suspension of anticoagulant therapy, of which 9 in the same location as the index event and 5 in the lower limbs. The overall relapse rate was 4.8%, with a peak of 6.4% within 18 months of the event. From a multivariate analysis for the clinical and anamnestic variables collected, only age over 50 years was found to be a risk factor for relapse with an OR of 5.2 (95% CI 1.5 - 18.7, p .010).
Conclusions: Despite the limitations of a retrospective study, we have collected a rather large population. From our data the safety and effectiveness of DOAC therapy emerge even if, to date, it does not have a formal indication for this type of thrombotic events, but which is often used in common clinical practice. The rate of recurrence of events in these patients is rather low, so routine long-term anticoagulant therapy does not seem desirable. However, the location of the relapses, often in the lower limbs, suggests an increased systemic thrombotic risk and not an isolated predisposition at the level of the upper limb circulation. A greater characterization of these events is certainly desirable to select patients at greater risk of recurrence.

CO067

OBSTETRIC HEMORRHAGE AND ANEMIA: DATA FROM MINNIE REGISTRY PROSPECTIVE STUDY ON FETO-MATERNAL OUTCOME IN ANEMIC WOMEN: MINNIE STUDY

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Background: Pregnancy-related mortality worldwide is mainly due to hemorrhage and venous thromboembolism (VTE).
Objectives: To estimate whether and to what extent antenatal hemoglobin is a risk factor for adverse obstetric outcomes.
Methods: MINNIE is a prospective observational study, that recruited consecutive pregnant women referred for delivery to three Ob/Gyn departments of tertiary care hospitals from January 2022 to March 2023. We collected maternal clinical and laboratory data along with feto-maternal outcomes. Maternal and fetal outcomes were also collected: maternal or fetal/neonatal death, venous thromboembolism, antepartum and peripartum (collectively defined as obstetric) hemorrhage, preterm deliveries, and neonatal birth-weight. Anemia was categorized into no anemia (hemoglobin 11 g/dL or greater), mild (9-10.9 g/dL), moderate (7-8.9 g/dL), severe (less than 7 g/dL).

Table 1.

Descriptive analysis of all women and according to the occurrence of obstetric hemorrhage.

	All N= 2176	Obstetric hemorrhage N= 30	No obstetric hemorrhage 2140	p
Age, median (IQR)	32.5 (28.4-36.1)	32.4 (30.6-37.1)	32.4 (28.4-36.1)	ns
BMI, median (IQR)	23.5 (21.1-27.1)	22.8 (20.7-27)	23.5 (21.1-27.1)	ns
Previous pregnancy, (%)	1112 (51.1)	13 (43.3)	1099 (51.4)	ns
Previous CS, (%)	350 (16.1)	4 (13.3)	346 (16.2)	ns
Previous VD, (%)	811 (37.3)	9 (30)	802 (37.5)	ns
Previous pregnancy loss, (%)	572	5	567	ns
ART conception, n	13	0	13	ns
LMWH in pregnancy, (%)	35	14	21	ns
ASA in pregnancy, (%)	15	1	14	ns
Hb at admission, median (IQR)	12 (11.0-12.7)	11.6 (10.7-12.02)	12 (11-12.7)	0.01
Hb at discharge, median (IQR)	11 (10.0-12-0)	9.4 (8.0-11.0)	11 (10-12)	<0.01
RBC at admission, median (IQR)	4120 (3870-4360)	4040 (3770-4275)	4120 (3870-4360)	ns
RBC at discharge, median (IQR)	3890 (3530-4220)	3260 (2880-3630)	3890 (3550-4230)	<0.01
Iron (n=1780), median (IQR)	70 (47-101)	69 (44-100.1)	70 (70-101)	ns
Ferritin (n=799), median (IQR)	11 (8-18)	13.5 (9.8-20.0)	11 (8-18)	ns
PT at admission , median (IQR)	1.1 (0.9-1.0)	0.9 (0.9-1.0)	0.9 (0.9-1.0)	ns
aPTT at admission , median (IQR)	0.9 (0.8-0.9)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	ns

CS: Cesarean section
ART: Assisted Reproductive Technique
LMWH: Low-Molecular Weight Heparin
ASA: Aspirin
Hb: Hemoglobin
IQR: Interquartile Range
RBC: Red Blood Cells

Results: We recruited 2176 women, whose characteristics are shown in Table 1. Among them, one deep venous thrombosis was recorded and 30 obstetric hemorrhage (13.4 per 1,000). Preterm delivery (before the end of 37 weeks) was significantly associated with maternal hemorrhage. As for anemia, 371 (17.0) had mild, 21 (1.0%) moderate and 4 (0.2%) severe anemia, respectively, with no observed difference in rates of preterm and cesarean deliveries between anemic and nonanemic patients. The intrapartum-postpartum blood transfusion rate was 2.6 per 1,000. Moderate and severe anemia were significantly associated with lower neonatal birth weight (p=0.026) but not intrauterine fetal demise or neonatal death.
Conclusions: In non-selected pregnancies, obstetric hemorrhage is associated with preterm delivery and lower birth weight, without any significant impact on intrauterine or neonatal death.

CO068

THE HETEROZYGOUS P.R854Q VARIANT IS RESPONSIBLE FOR THE CONFORMATIONAL CHANGES IN THE D'D3 DOMAIN OF THE VON WILLEBRAND FACTOR, BY WEAKENING ITS INTERACTION WITH FACTOR VIII: IN-SILICO ANALYSIS

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Background and Aims: The recessive von Willebrand Disease (VWD) type 2N is caused by gene mutations in the region of the von Willbrand Factor (VWF) coding the D'D3 domain, the binding domain for the Factor VIII (FVIII). The homozygous variants, usually associated with severe bleeding diathesis, are characterized by the association between a reduction in the VWF plasma levels and low FVIII levels, due to alterations in the VWF-FVIII binding. Nevertheless, heterozygous variants cause a VWD type 2N with mild bleeding diathesis. The VWF p.R854Q variant has been found in about half of these patients. Hence, this study aim is to in-silico analyze the changes in the conformation of the VWF D'D3 domain and its interaction with FVIII, due to the p.R854Q heterozygous variant.
Methods: I-TASSER server, using the "6n29" pdb file as a template, predicted models of the D'D3 domain (S764-G1241) for the VWF WT and the p.R854Q variants. The human FVIII-(BDD) structure was derived from the "2r7e" pdb file (A1-A2-A3-C1-C2-domains), while the docking was performed through ClusPro server. The energetics of the VWF-FVIII binding was calculated with PRODIGY program. PROCHECK, PDBsum and Pymol programs were used for model validation and rendering.

Results: The glutamine residue in position 854 removes the polar interactions of the arginine 854 with V850, D860 and T859, disrupting the T848-W856 α-helix and forming two antiparallel β-strands. These conformational transitions generate allosteric rearrangements of the entire D'D3 domain structure (Figure 1). Thus, the VWF p.R854Q-FVIII binding results altered, since fewer amino-acidic residues of the VWF are involved (7 *VS* 29). Compared to the VWF WT form, the p.R854Q variant binding affinity for the FVIII was significantly lower (ΔΔG ≃10 kcal/mol).
Conclusions: This in-silico analysis shows that the arginine in position 854 could stabilize a correct conformation of the VWF D'D3 domain. Thus, the p.R854Q variant, though heterozygous, could cause structural transitions, reducing the VWF binding affinity for the FVIII and increasing its clearance.

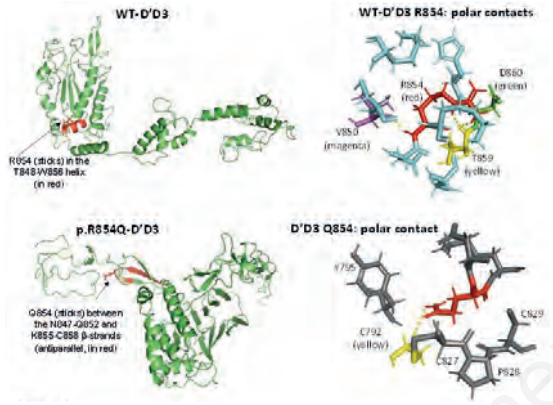

Figure 1.

CO069

NOVEL INSIGHT INTO THE GENETIC BACKGROUND OF LOW VWF USING WHOLE EXOME SEQUENCING

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Background: Low von Willebrand factor (VWF) refers to subjects with plasma levels of 30-50 IU/dL. The genetic background of Low VWF is poorly understood, with most cases not possessing VWF pathogenic variants.
Aim: To investigate the genetic background of Low VWF using whole-exome sequencing (WES).
Methods: Of 250 patients from the Low VWF Milan Cohort (LOVMIC), we have performed so far, WES for 71 patients and 150 healthy controls. Genetic association for common variants was performed using PLINK. For rare variants, a cumulative test using KGGseq (Burden, SKAT, and SKATO tests) was performed. Previously reported common variants associated with VWF levels were assessed by linear regression. Copy number variation (CNV) was performed by custom pipeline using CNVkit.
Results: *VWF* pathogenic variants (n=18) were found in only 19 patients (27%) however, 73% did not carry pathogenic variants. In the remaining 52 cases, 14 other genes known to be associated with VWF levels were investigated (*UFM1, AVPR2, LRP1, ST3GAL4, SCARA5, ABO, ACE, FUT1, STX2, CLEC4M, FUT2, ADGRB3, STXBP5, and STAB2*). We found 114 rare variants in these/and *VWF* genes with CADD score>15, affecting 116 alleles (26 cases, 90 controls) and the cumulative test indicated 2 significant genes (UFM1 and AVPR2). We found 16 common variants in *VWF* and other genes with a significant distribution between patients and controls ($p<0.05$, ABO-adjusted). Linear regression analysis on 6 previously reported variants (rs1063857, rs868875, rs2277998, rs1039084, rs9390459, and rs8176719) in 52 patients indicated that 3 of them have a significant association with VWF antigen levels (rs1063857: reduced level, rs868875 and rs2277998: increased level). CNV analysis identified 2 potential duplications in 2 patients and 2 deletions in the other 4 patients.
Conclusions: These novel results show that genes outside the *VWF* could be involved in the underlying mechanism of Low VWF patients without *VWF* pathogenic variants. Our results also newly indicate the relevant role of CNV in the genetic background of Low VWF.

CO070

TYPE 2M/2A VON WILLEBRAND DISEASE: A SHARED PHENOTYPE BETWEEN TYPE 2M AND 2A

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Background: Four frequently reported *VWF* variants have been subjected to debate and received different von Willebrand disease (VWD) classifications: p.R1374H, p.R1374C, p.R1315L, and p.R1315C.
Aim: To deeply investigate and characterize p.R1374H, p.R1374C, p.R1315L, and p.R1315C variants with a full

panel of VWD tests, protein modeling predictions, and structural biology.
Methods: Forty-three patients with p.R1374H, p.R1374C, p.R1315L, and p.R1315C were included. In addition, 70 patients with typical type 2A (n= 35) or 2M (n= 35) were included to understand their similarities and differences. Patients were investigated for phenotypic assays and underlying disease mechanisms. We further applied deep protein modeling predictions and structural biology using Molecular and Langevin dynamics and AlphaFold2 to elucidate the effects of these variants on the VWF A1-A2 domains.
Results: Variant p.R1315C clearly represented a type 2M phenotype. However, p.R1374H, p.R1374C, and p.R1315L patients showed a common phenotype between VWD type 2M and 2A using VWF activity/VWF:Ag and VWF:CB/VWF:Ag ratios and VWF multimeric profile. VWF synthesis/secretion was reduced in 2M and in p.R1374H, p.R1374C, and p.R1315L cases, but not in type 2A. Reduced VWF survival was observed in most 2A (77%) and 2M (80%), and all 40 cases (100%) with p.R1374H, p.R1374C, and p.R1315L. Since the mutual spatial arrangement of the A1-A2 and the overall system dynamic is unknown, we newly developed it in this study. These were the only variants that fall at the interface between the A1-A2 domains. The mutants of residue R1315 induce more compactness and increased internal mobility but residue R1374 displays more extended A1-A2. Our analysis revealed that the pathological common trait can be related to the accessibility of sensibly populated states, the exploration of which is induced by mutations.
Conclusions: We propose a new classification for p.R1374H, p.R1374C, and p.R1315L as VWD type 2M/2A because they share a common phenotype between type 2A and 2M. Structural analysis indicates the unique location of these variants on the A1-A2 domain and their distinctive effect on VWF.

CO071

HETEROGENEOUS VWD PHENOTYPES STEMMING FROM ALTERED VWF MRNA SPLICING C.3538+1G>T, C.5455+1G>A AND C.3108+1G>A PATHOGENIC MUTATIONS

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A large proportion of type 1 von Willebrand disease (VWD) cases are associated with missense mutations scattered over the entire von Willebrand factor (VWF) gene. A few mutations are caused by heterozygous stop codon or splice site mutations. In these subjects typically VWF levels of 30 – 50 U/dL are observed, bleeding history is mild or absent and they are usually considered as carriers for type 3 phenotypes. We report the clinical phenotypes of three families with heterozygous splicing mutations associated with significantly reduced FVIII and VWF levels. Two mutations have been previously demonstrated to be associated with in-frame skipping of exons 26 (c.3538+1G>T) and 31 (c.5455+1G>A), while c.3108+1G>A is predicted to cause exon 23 skipping. All the patients showed variable baseline increase of VWFpp/VWF:Ag ratio (>3; normal range <1.6), suggesting an increased VWF clearance. Bleeding tendency was significant in all patients (Bleeding score >6). Desmopressin showed a complete response for c.3538+1G>T and c.5455+1G>A subjects, but with a rapid return to baseline in keeping with the hypothesized increased VWF clearance. Subjects with c.3108+1G>A variant had complete FVIII response but VWF reached a 50 U/dL levels only. Pregnancy in women with c.5455+1G>A and c.3108+1G>A variants induced a significant increase of FVIII, but VWF showed a minimal increase only. In conclusion, as for classical variants with increased VWF clearance (e.g, p.Arg1205His, Type Vicenza), also heterozygous splicing mutations can cause a markedly reduction of VWF with increased VWF clearance evident at baseline and also after a desmopressin trial. Similarly, pregnancy is not able to produce sustained correction of VWF and these women requires management with VWF-containing concentrates. These data further confirms the wide heterogeneity of VWF gene mutations underlying similar clinical and laboratory phenotypes.

CO072

GENETIC BACKGROUND AND CLINICAL IMPACT OF TYPE 3 VON WILLEBRAND DISEASE IN TUSCANY

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Type 3 von Willebrand disease (VWD) is the rarest subtype of the disease, whose clinical impact has been overlooked in the past. The presence of joint bleeding, similarly to that reported in the moderate/severe forms of hemophilia, is now considered mandatory for starting appropriate prophylaxis with von Willebrand factor (VWF) concentrates. However, several of these patients have already developed clinical and radiological signs of chronic arthropathy. We report the genetic background and its relationship with orthopedic outcome in a cohort of patients with type 3 VWD followed at our center. Twelve patients (6 F, 6 M) with

type 3 VWD have been included (Table 1). All had severe VWF deficiency (<2 U/dL) and severe FVIII deficiency (usually between 1-5 U/dL, apart 2 cases). VWF propeptide was 1 mU/mL (NR >50 mU/mL) in all the patients. Eight patients were homozygous for null mutations, no missense mutations were detected in any of the patients. The c.7630 C>T Gln2544* was present in two homozygous and two compound heterozygous patients, all unrelated and of Tuscany origin. Two unrelated Chinese patients reported a homozygous c.7599 T>A Cys 2533* mutation, previously reported in the Chinese population. Two patients had partial gene deletion, homozygous and in compound heterozygosity. None of the patients have anti-VWF inhibitors. Overt radiological and ultrasound evidence of arthropathy was present in 7/12 and all these patients are on prophylaxis, apart from a single patient who refused it. In conclusion, these type 3 VWD patients have all null mutations preventing complete VWF synthesis, a phenotypically severe disease and a significant proportion shows severe arthropathy requiring long-term prophylaxis. Early starting of prophylaxis is recommended in VWD patients with joint bleeding, especially at younger age.

Table 1.

Clinical and laboratory features of type 3 VWD

SEX, age	EXON	MUTATION	FVIII:C (U/dL)	VWF:Ag (U/dL)	VWF:RCo (U/dL)	Overt Arthropathy
M, 40	25	IVS25+1 G>T homozygous	1-5	<2	<2	Right elbow joint replacement at age 24, on prophylaxis
F, 72	45	c. 7630 C>T Gln2544* homozygous	1-5	<2	<2	Deceased, knee arthropathy, on prophylaxis for GI bleeding
F, 32	45	c. 7599 T>A Cys2533* homozygous	1-5	<2	<2	
M, 47	28	c. 4944 DelT Pro1648Profs*45 heterozygous	1-5	<2	<2	Bilateral elbow and right ankle arthropathy, on prophylaxis
	19	IVS18-1 G>C heterozygous				
M, 30	36	c. 6387-8 DelC Pro2063HisfsX36 homozygous	1-5	<2	<2	right ankle arthropathy, synovectomy at age 21. Refuse prophylaxis
M, 54	45	c. 7630 C>T Gln2544* homozygous	1-5	<2	<2	Bilateral elbow and ankle severe arthropathy, on prophylaxis
F, 44	45	c. 7630 C>T Gln2544* heterozygous	5	<2	<2	
	16	IVS 15-4 (c. 1946-4) C>T heterozygous				
F, 44	45	c. 7630 C>T Gln2544* heterozygous	5	<2	<2	
	16	IVS 15-4 (c. 1946-4) C>T hetero				
M, 37	45	c. 7599 T>A Cys2533* homozygous	1-5	<2	<2	Right knee arthropathy, on prophylaxis
F, 34	18	c.2435delC Pro812ArgfsX31homozygous	1-5	<2	<2	
F, 26	28	Gln1311* heterozygous Ex1-6Del heterozygous	1-5	<2	<2	Left ankle, elbow, and knee arthropathy, on prophylaxis
M, 58	17	c.2187-1185_2283+74 del homozygous	1-5	<2	<2	Shoulder and ankle arthropathy, on prophylaxis

CO073

OUTCOMES OF HIGH AND INTERMEDIATE-HIGH RISK PULMONARY EMBOLISM IN ONCOLOGIC AND NON-ONCOLOGIC PATIENTS UNDERGOING CATHETER DIRECTED THROMBOLYSIS: AN INDIVIDUAL PATIENT LEVEL ANALYSIS

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Background and Aims: Pulmonary embolism (PE) represents a common burden of morbidity and mortality in patients with cancer. Catheter directed thrombolysis (CDT) and percutaneous mechanical thrombectomy have been developed as options to treat high or intermediate-high risk PE. However, outcomes of percutaneous treatment in oncologic patients with PE have not been thoroughly investigated. We aim to evaluate effectiveness and outcomes of CDT in high or intermediate-high risk PE in patients with active or previous cancer, comparing with non-oncologic patients.

Methods: The medical literature published before December 2022 was systematically reviewed. Sixteen observational studies and randomized trials of CDT-based therapies for high and intermediate-high risk acute PE were identified. To be included, patients had to present an acute high or intermediate-high risk PE, to be older than 18 years and to have received a CDT as primary treatment.

Results: On a total of 1171 patients with PE included, 137 of them (11.7%) had active or previous history of cancer. Among them, 10.9% had an high-risk PE. Oncologic patients were slightly older (median age 65 years old, Q1-Q3: 57-74) and with a lower body mass index (BMI) (median BMI 32.3 kg/m², Q1-Q3 25.9-34.1) compared with non-oncologic patients (median age 60 years old, Q1-Q3 48-70; median BMI 32.3 kg/m², Q1-Q3 27.6-38.3). No significant differences were observed between the two groups in terms of comorbidities, clinical features and laboratory test at presentation. CDT treatment was associated with a significant improvement (p<0.001) in pulmonary pressures (systolic, diastolic and mean) and in right ventricular function. Overall, the mean pulmonary artery pressure (mPAP) in patients with cancer decreased from a median of 31.9 mmHg (Q1-Q3: 26.4 – 38.6) before treatment to a median of 21.8 mmHg (Q1-Q3: 17.0 – 26.1) after treatment; no significant differences were found between oncologic and non-oncologic patients. Oncologic patients exhibited higher in-hospital (7.63% *vs* 2.36%, OR 4.09) and 30-day (5.05% *vs* 1.28%, OR 2.8) mortality rates, compared to non-oncologic ones (Table 1). Instead, there wasn't a significant difference in the risk of major intracranial bleeding nor hemodynamic decompensation. Patients with cancer showed a non-significant tendency towards longer in-hospital stay (median 7.9 days) compared to non-oncologic patients (median 6.6 days) (p 0.064). Older age (>75 years old) was an overall predictor of adverse outcomes: among non-oncologic patients, it was associated with an increased risk of major bleeding and in-hospital and 30-day-death, while in cancer patients it was associated with an increased in-hospital death (p 0.046).

Table 1.

	Total	Cancer	No cancer	OR (95% CI)	P value
Hemodynamic decompensation	50/817 (6.12%)	2/95 (2.10%)	48/722 (2.36%)	0.89 (0.20-3.92)	0.880
Major bleeding	56/1034 (5.42%)	8/123 (6.5%)	48/911 (5.27%)	1.25 (0.58-2.71)	0.570
Intracranial bleeding	5/804 (0.62%)	1/103 (0.97%)	4/701 (0.57%)	1.71 (0.19-15.44)	0.629
Death 30 days	39/1141 (3.42%)	10/131 (7.63%)	29/1010 (2.36%)	**2.80 (1.33-5.88)**	**0.005**
In-hospital death	15/877 (1.71%)	5/99 (5.05%)	10/778 (1.28%)	**4.09 (1.37-12.21)**	**0.007**

Conclusions: In patients hospitalized with high or intermediate-high risk PE and undergoing CDT, active or previous cancer is an independent risk factor for in-hospital and 30-day mortality, compared with non-oncologic patients. No differences were found in bleeding complications or hemodynamic decompensation. Prospective randomized controlled trials including patients with cancer are needed to confirm our findings.

CO074

FACTOR VIII A COAGULATION CO-FACTOR IS A RELEVANT SURVIVAL FACTOR IN BLADDER CANCER CELLS

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Background: Factor VIII (FVIII), an essential coagulation co-factor and independent cancer associated thrombotic risk factor, has recently been shown to be synthesized directly by a broad profile of cancers. With evident extra-coagulative functions, it remains to be understood if FVIII can play a functional role in cancer. Using bladder cancer cell models, the aim of the present study was to determine if FVIII can play a direct role in cancer.
Methods: The 5637 and ECV-304 bladder cancer cell lines were treated with 1U/ml recombinant human FVIII B-domain deleted (rFVIII-BDD) or full length (rFVIII-FL) in low serum conditions (0.5%FBS), where cell cycle, migration, and cell survival were assessed. Cell cycle was evaluated by flow cytometry (FACS) at 24hr for 7-Aminoactinomycin D (7-AAD) incorporation, and migration at 18hr by Transwell or wound-healing assays. Cell survival was assessed by crystal violet staining (CV;OD592) and metabolism by 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide (MTT;OD570). Apoptosis by Annexin-V-FITC/7-AAD staining, with Bcl2 and procaspase3 protein levels by western blot. Cancer cell-derived FVIII was tested by silencing FVIII expression in 5637 cells using short hairpin RNA (shFVIII;n=3).
Results: The two forms of rFVIII modestly pushed cell cycle progression at 24hr, with rFVIII-FL attributing to a significantly lower% of cells in G0-G1 for ECV-304 ($p<0.05$) and a higher% in G2-M for 5637 cells ($p<0.05$). Migration advanced with rFVIII-FL increasing 1.89-fold ($p<0.05$) for 5637 cell and 1.94-fold ($p<0.05$) for ECV-304, with intermediary results for rFVIII-BDD. More significant, however, were the evident survival effects seen in the presence of rFVIII-FL when compared to 0.5%FBS, with 3-fold ($p<0.01$) higher viability at 6dys for 5637 cells and 1.3-fold higher ($p<0.001$) for ECV-304, with intermediary results for rFVIII-BDD. Metabolic activity supported the increased viability. Cancer cell survival was achieved through the inhibition of apoptosis. Annexin5/7-AAD staining of 5637 cells treated with rFVIII-FL at 6dy identified 76.4±3.6% LIVE cells, 7.4±0.9% in early apoptosis (EA) and 11.8±2.2% in late apoptosis (LA), while cells in 0.5%FBS were 44.6±8.7% LIVE, 13.8±1.7% in EA and 25.8±8.2% in LA, with rFVIII-BDD showing intermediary results. In support, Bcl2 and procaspase3 (Procasp3) protein levels were sustained over time in rFVIII-FL treated 5637 cells, while levels dropped significantly for 0.5%FBS (Bcl2, 3.5-fold [$p<0.01$]; Procasp3, 2.1-fold [$p<0.01$]) and rFVIII-BDD (Bcl2, 1.9-fold [$p<0.05$]; Procasp3, 1.8-fold [$p<0.01$]) treatments at 8dys. Importantly, the silencing of 5637-cell derived FVIII retarded cell cycle progression at 24hr with more cells in G0-G1 than control (73.6 *vs* 62.5%; $p<0.0001$) and less in G2-M (14.7 *vs* 26.7%; $p<0.0001$). Further, wound-healing assays highlighted as early as 6.5hr a slower migration for shFVIII. More importantly, however, 5637-shFVIII cell survival was dramatically reduced being 2-fold lower ($p<0.0001$) at 6dys, which in turn could be rescued by the administration of rFVIII-FL.
Conclusions: This pilot investigation highlights FVIII as a survival factor in bladder cancer cells and provides early evidence of a direct role in cancer-related pathophysiology. It remains to be understood the impact on cancers of diverse origin, however, these observations support the concept that targeting FVIII may offer a potential novel therapeutic target for bladder cancer patients.

CO075

SUPERFICIAL VEIN THROMBOSIS AND OCCULT CANCER: THE TVS-CANCER STUDY

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Introduction: Cancer is associated with a prothrombotic state and venous thromboembolism (VTE) can be the first manifestation of occult cancer. However, limited data are available on the association between superficial vein thrombosis (SVT) and occult cancer.
Objectives: To investigate whether SVT is associated with subsequent cancer development.
Design: retrospective cohort conducted in a single tertiary care hospital from 2005 to 2020. Participants: consecutive patients diagnosed with symptomatic SVT and without overt cancer underwent routine clinical evaluation, laboratory tests and received antithrombotic treatment. Primary outcome measures: cancer development during follow-up after SVT diagnosis.
Results: 309 patients (200 women - 65%, median age 70.1 years; 3 lost to follow-up -1%) were included of which 57 (18%) occurred in the absence of varicose veins. During follow-up, 32 patients (10%) developed new cancers (28 in the presence of varicose veins - 9%-

and 4 in the absence of varicose veins -7%). Cancer developed in 11 patients with recurrent T*VS* beyond 12 months (46-24%) and in 21 patients without a recurrent T*VS* (251- 8.3%) (p=0.004). Multivariate regression showed that only recurrent T*VS* was independently associated with subsequent cancer development (HR: 2.94; 95% CI: 1.5-7.6; p=0.004).
Conclusions: Patients with recurrent T*VS* may deserve screening for occult cancer, regardless of the presence or absence of varicose veins.

CO076

RETRIEVABLE INFERIOR VENA CAVA FILTER USE IN CANCER PATIENTS WHEN COMPARED TO NON CANCER PATIENTS

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Introduction: inferior vena cava filters (IVCF) are employed in patients with venous thromboembolism (VTE) when there is an absolute contraindication to anticoagulation. Their use has increased with the availability of retrievable IVCF.
Objectives: To investigate the indications for IVCF, the retrieval rates and complications in cancer patients when compared to non cancer patients
Design: Retrospective cohort conducted in a single tertiary care hospital from 2018 to 2020. Participants: consecutive patients diagnosed with symptomatic VTE (either pulmonary embolism or deep vein thrombosis (DVT) and undergoing retrievable IVCF placement from 2018 and 2021.
Primary outcome measures: Indication for IVFC, retrieval rates and complications.
Results: 323 patients (168 women - 53%, median age 75 years) were included of which 152 (47%) had an active cancer, 53 (16.4%) had intracranial haemorrhage, 73 (22%) had major bleeding (gastrointestinal in 31, other sites in 42), 46 (14.4%) for other reasons (35 for high bleeding risk). Preoperative IVCF was implanted in 153 patients (47%) of whom 104 had an active cancer. During follow-up, IVFC was removed successfully between 3 and 75 days in 137 patients (42%), of whom 73 were cancer patients (48%), 6 had intracranial haemorrhage (11%), 9 (30%) had gastrointestinal bleeding, and 96 (62%) had IVFC placed preoperatively. Filter thrombosis was observed in 36 patients in whom retrieval was attempted (26%) and in 17 retrieval was not possible (15 were cancer patients) while thromboaspiration was performed with retrieval in the remaining. At 24 months 165 patients (51%) died of whom 75 (45%) for cancer.
Conclusions: Cancer patients were the majority of patients in whom IVCF were placed with a high mortality rate. Filter thrombosis was a frequent complication especially in cancer patients.

CO077

A RISK PREDICTION MODEL BASED ON FXI-ANTITHROMBIN FOR VENOUS THROMBOEMBOLISM (VTE) IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: VTE is a frequent complication in ambulatory lung cancer patients, especially during chemotherapy. However, identifying high-risk patients who may benefit from thromboprophylaxis is still a challenge for clinicians, as validated VTE risk assessment models (RAMs) still present some limitations. Recent studies have shown that the contact system of coagulation may play a role in the development of thrombosis in cancer. However, limited data are available on the relationship between the activation of the contact system and VTE in NSCLC patients.
Aim: In a prospective outpatient cohort of NSCLC patients starting chemotherapy, we measured the levels of biomarkers of contact system activation to assess whether they can help predict VTE within 6 months after starting chemotherapy.
Methods: Patients with a new diagnosis of advanced NSCLC starting chemotherapy enrolled in the HYPERCAN study were evaluated. Prechemotherapy plasma samples were tested by ELISA for *in vivo* biomarkers of both contact system activation and thrombin generation. Specifically, biomarkers of contact system activation evaluated were prekallikrein: antithrombin [PKa:AT], activated FXI:AT [FXIa:AT], FXIa: C1-esterase inhibitor [FXIa:C1Inh], and FIXa:AT complexes. Prothrombin fragment 1+2 [F1+2] and thrombin-antithrombin [TAT]

complex were evaluated as biomarkers of thrombin generation. Clinical data and VTE were prospectively recorded.
Results: A cohort of 719 newly diagnosed NSCLC patients (489M/230F), with a median age of 66 years (SD 9.5), were studied. Stage disease was metastatic in 568 and locally advanced in 151 patients. After 6-month follow-up, the cumulative incidence of VTE was 10% in the whole cohort, 12% in metastatic, and 4% in the locally advanced group. Patients who developed VTE (n=68) were characterized by significantly ($p<0.001$) higher basal levels of FXIa:AT, F1+2, and TAT, compared to VTE-free patients, even after correcting for age and gender. By multivariable analysis, FXIa:AT [HR 1.18 (95%CI 1.02-1.39)] and TAT [HR 1.30 (95%CI 1.08-1.57)] were identified as independent risk factors for VTE. A continuous score based on these two biomarkers was developed. The Kaplan Meyer analysis showed that patients with FXIa:AT and TAT values above the highest quartile of the score had a significantly higher incidence of VTE than those with values below the 3rd quartile (23% *vs* 8%, log-rank <0.001).
Conclusions: According to our research, patients with NSCLC who developed VTE displayed higher biomarker levels of contact system activation and thrombin generation. These biomarkers were useful to create a scoring system that allowed the identification of patients at a three-fold higher risk of developing VTE during chemotherapy. Our findings suggest a link between the activation of the contact pathway and the hypercoagulable state in lung cancer patients, supporting the use of a thromboprophylaxis strategy based on FXIa inhibitors in this setting.

CO078

DIRECT ORAL ANTICOAGULANTS FOR PREVENTION OF VENOUS THROMBOEMBOLISM AFTER CANCER-RELATED SURGERY: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Background and Aims: The risk of venous thromboembolism (VTE) is particularly high after cancer surgery and it IS reduced by antithrombotic prophylaxis. The efficacy and safety of direct oral anticoagulants (DOACs) in this setting remain debated. This study aimed to evaluate the effectiveness and safety of DOACs for VTE prophylaxis after cancer surgery.
Methods: Randomized controlled trials (RCTs) and non-randomized studies (NRSs) reporting on VTE events and/or bleeding complications and/or death in patients receiving DOACs for prophylaxis of VTE after cancer surgery were included. A frequentist network meta-analysis (NMA) was conducted to estimate the pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs).
Results: Five RCTs (1694 patients) and 7 NRSs (2042 patients) were included in the analysis. When all the studies were considered, regardless of the timing for DOACs initiation, prophylaxis with apixaban (OR 0.12, 95% CI 0.02-0.73) and not with rivaroxaban (OR 0.26, 95% CI 0.07-1.04) or low molecular weight heparin (LMWH) (OR 0.38, 95% CI 0.08-1.76) significantly reduced the risk of VTE at 30 days from surgery compared with placebo/no treatment. Apixaban (OR 0.31, 95% CI 0.11-0.84) and not rivaroxaban (OR 0.69, 95% CI 0.35-1.34) was associated with significant reduction in VTE at 30 days in comparison to LMWH. No significant difference in 30-day VTE was found with apixaban *vs* rivaroxaban (OR 0.45, 95% CI 0.13-1.49). Compared to placebo/no treatment, Apixaban and LMWH prophylaxes were significantly associated with increased risk of clinically relevant bleeding at 30 days from surgery.
Conclusions: Our study in post-operative prophylaxis of VTE after cancer surgery supports apixaban and rivaroxaban as promising alternatives to LMWH despite further high-quality data being needed in specific surgical settings.

CO079

RESIDUAL PLATELET ACTIVATION IN CHRONIC CAD PATIENTS WITH DEPRESSION

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Background and Aims: Depression is associated with cardiovascular events and it predicts mortality more than any other risk factors, comorbidity or follow-up events, suggesting that the standard antiplatelet therapy may not be sufficient to prevent the poor prognosis in patients with this pathological condition. Despite increasing evidence suggests the relationship between platelet activation and cardiovascular/depression comorbidity, to our knowledge, no specific study has been carried out to assess the effect of depression on standard anti-platelet therapy in coronary artery disease (CAD) patients. Here, we have examined whether chronic CAD patients with depression on standard aspirin treatment have hyperreactive platelets and whether a relationship between platelet function and circulating brain derived neurotrophic factor (BDNF), a surrogate marker of depression, exists.
Methods: 232 chronic CAD patients on standard

aspirin treatment were evaluated for depression (BDI-II) and ninety-six (37 depressed and 59 non depressed) were enrolled. Clinical profile was assessed at the enrollment and platelet reactivity was evaluated in terms of: aggregation in platelet rich-plasma induced by collagen, ADP, TRAP, and serotonin (Born's method); P-selectin exposure, GPIIbIIIa activation, and ability to bind leukocytes, monocytes and neutrophils in whole blood, and calcium movement in washed platelets (flow cytometry). Serum thromboxane metabolite was quantified by LC-MS/MS method. Plasma and serum BDNF levels were measured by ELISA kit. Data were analyzed using the SAS software package v. 9.4. Comparisons between groups were made using general linear models adjusted for age and sex, after transformation (log or Box-Cox) of variables with skewed distribution. All tests were two-sided, a P value <0.05 was required for statistical significance. Spearman's correlation coefficient was calculated.

Results: CAD patients with depression displayed a higher residual thromboxane formation in serum compared to CAD (P<0.007). In these patients, we have found an enhanced platelet aggregation in response to different dose of collagen (0.5, 1, 2 and 4 mg/L; P<0.01), ADP (0.5, 1 and 2 µM, P<0.03) and TRAP (4 µM; P<0.01), but similar response to serotonin and epinephrine, and an increased percentage of platelet/leukocyte (P<0.0001), platelet/monocyte (p<0.02) and platelet/neutrophil (P<0.02) aggregates compared with CAD patients. CAD patients with depression displayed also an abnormal platelet calcium homeostasis (P<0.02). BDNF plasma and serum levels as well as the BDNF serum/platelet ratio (P<0.002) were lower in patients with depression, which suggests a reduced BDNF platelet starvation in these patients. Interestingly, a positive correlation between BDNF levels and platelet count was found only in CAD patients without depression (r:0.398; P<0.002), whereas circulating BDNF correlated positively with platelet activation markers in depressed CAD patients (P<0.05).

Conclusions: Our study highlights the presence of hyper-reactive platelets associated with lower BDNF levels in chronic CAD patients with depression. The residual thromboxane production and platelet activation observed in chronic CAD patients with depression open the question if standard antiplatelet therapy with aspirin is sufficient to prevent platelets activation and potential thrombotic events in this clinical setting.

CO080

MUTATIONS IN SMAD3 GENE: RELATIONSHIP WITH CARDIOVASCULAR FEATURES

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Background and Aims: SMAD3 gene encodes a component of the TGFβ-signaling system and is associated to Loeys-Dietz syndrome (LDS) and natural history for aortic dissection at smaller aortic diameter and arterial aneurysms. In this study we have explored the relationship between rare genetic variants identified in SMAD3 gene and the clinical phenotype in subjects attending the Regional Referral Center for Marfan syndrome and Related Disorders (Careggi Hospital, Florence) for differential diagnosis.

Methods: Targeted Next Generation Sequencing (NGS) approach of at least 17 genes associated with aortopathy (ACTA2, CBS, COL3A1, ELN, FBN1, FBN2, LTBP3, MYH11, MYLK, SKI, SLC2A10, SMAD2, SMAD3, TGFB2, TGFB3, TGBR1, TGFBR2) has been performed thought SureSelectQXT library preparation kit (Agilent Technologies) on MySeq Illumina platform. Segregation analyses of variants identified in available family members has been carried out through Sanger technology.

Results: Among 327 patients analysed, seven rare variants in SMAD3 gene have been identified in 6 (4 males and 2 females, 1.8%, mean age 57.5 years): an intronic variant and six missense variants. Actually, two strictly adjacent missense variants [c.1028T>A (p.Phe343Tyr) and c.1029C>A (p.Phe343Leu)] have been found in the same subject that, if present in cis, cause protein truncation (p.Phe343Ter). The segregation analysis in family members has allowed to confirm the presence in cis of these variants and in turn the creation of a premature stop codon. Four variants identified in 4 out of the 6 subjects are located in exons 6 and 8, both encoding the MH2 domain; really, data from literature reported that individuals with dominant negative SMAD3 variant in the MH2 domain exhibited more major events occurring at a younger age compared to those with haploinsufficient variants (Nathalie P de Wagenaar *et al.,* 2024). Among these subjects, 2 had type A aortic dissection, 1 open surgery for abdominal aortic aneurysm and ascending aortic replacement surgery, and the last subject had spontaneous coronary dissection as a result of a coronary angioplasty intervention. Among other subjects, one had a splicing variant in intron 7 (c. 1009+2T>C) and underwent mitral valvulopastics for mitral cord rupture, and exhibited root ectasia, ascending aorta replacement, right subclavian aneurysm, right bronchial and intercostal arteries aneurysms, splenic artery and iliac arteries. The last subject in whom a SMAD3 variant has been identified is a subject with a missense variant located in the MH1 domain, who clinically presented aortic dissection, dilated cardiomyopathy and heart failure. The segregation analysis in family members has evidenced that the variant in SMAD3 has been transmitted to daughters who have mitral valve prolapse with mitral ring disjunction (MAD) associated with arrhythmia and cardiomyopathy, supporting the segregation of SMAD3 variant with the clinical phenotype. Correlation between pathogenic variants in SMAD3 and heart failure are already described in the literature (Julie De Backer *et al.,* 2018) (Table 1).

Conclusions: Obtained results highlight the relevance of molecular characterization in subjects with aortopathy in order to provide diagnosis definition, risk stratification, and to establish an appropriate therapeutic management in patients.

Table 1.

ID	Location	Variants	MAF (Eur)	ACMG	SNP Id (rs)
2493	chr15:67473780:G:A	c.[860G>A];[=]. p.[Arg287Gln];[=]	NA	P	rs730880214
2628	chr15:67457264:C:T	c.[2338C>T];[=]. p.[Arg780Trp];[=]	NA	LP	rs750707381
3102	chr15:67479826:A:G	c.[1133A>G];[=]. p.[Lys378Arg];[=]	NA	LP	NA
2953	chr15:67477204:T:C	c.[1009+2T>C];[=]	NA	LP	NA
2902	chr15:67473721:TC:AA	c.[1026_1029delTCinsAA];[=]. p.[Phe343Ter];[=]	NA	LP	NA
3070	chr15:67473772:T:G	c.[1079T>G];[=]. p.[Phe360Cys];[=]	NA	LP	NA

CO081

HYPERCHOLESTEROLEMIA: GENETIC PROFILE AND CARDIOVASCULAR DISEASE

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Background and Aims: Many familial hypercholesterolemia (FH) subjects (about 60%) did not demonstrate functional mutations in major candidate genes (LDLR, APOB, PCSK9, LDLRAP1). According to this observation, we assessed FH patients genetic profile by high-throughput sequencing (HTS).
Methods: We analysed 129 FH patients [adults with possible/probable/definite FH according to Dutch Lipid Clinic Network Score (DLCN)]. Targeted HTS (57 genes involved in lipid metabolism, supposed to be involved in dyslipidaemia, pharmacogenetics of statins, related to FH polygenic forms, HDL and triglycerides related diseases) was assessed by Illumina technology.
Results: Among 129 patients [83 females and 46 males, age median (IQR): 50 (17-60)], 52 (40%) carried a rare variant in LDLR gene [42 (33%) carrying a likely pathogenic/pathogenic (LP/P) variant, 6 (5%) carrying an uncertain significance variant (VUS), and 4 (3%) carrying a likely benign/benign variant (LB/B)]. Talmud score evaluation (Talmud 2013) showed a significantly higher median value in patients LDLR-negative for the presence of a VUS or LP/P variant, with respect to LDLR-positive [median(IQR): 1.015(0.897-1.090) *vs* 0.887 (0.754-1.038), p=0.012]. Ten out of the 48 LDLR-positive patients also carried a rare variant in another FH-associated gene. In patients without LDLR mutation, at least 2 rare variants were identified in 44 patients (54%), and at least 3 rare variants were identified in 31 patients (38%). In these patients, a total of 170 rare variants have been identified in 41 different genes (ABCA1, ABCB1, ABCG2, ABCG5, ABCG8, ANGPTL3, APOA4, APOA5, APOB, APOC3, APOE, CELSR2, CREB3L3, DAB2, EPHX2, GCKR, GHR, GPD1, HFE, HMGCR, INSIG2, ITIH4, LDLRAP1, LIPC, LIPI, LMF1, LPA, LRP1, MTTP, NPC1, NPC2, NYNRIN, PCSK9, PON1, PPP1R17, SCARB1, SLC22A1, SLCO1B1, SREBF1, SREBF2, ST3GAL4). Among FH patients, 32 were younger than 18 yrs. Among adults, LDL-cholesterol levels were comparable between LDLR-positive and LDLR-negative group, whereas in younger subjects significantly higher LDL-cholesterol levels were observed among LDLR-positive. As concerns DLCN score, performed in adult population, significantly higher values in subjects carrying LDLR mutation were found.
Conclusions: Present data suggest the involvement of multiple loci beyond LDLR gene in the modulation of lipid profile, as well as cardiovascular risk. Nevertheless, the expansion of genetic analysis to a largest cohort might allow a better comprehension of the role of further major/modifier genes, as well as of accumulation of common small- effect LDL-C raising alleles in determining LDL-C levels and cardiovascular events.

CO082

INTERINDIVIDUAL VARIABILITY RESPONSE IN PLATELET AGGREGATION IN PATIENTS ON ASPIRIN THERAPY: INSIGHTS FROM A RETROSPECTIVE ANALYSIS

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Background and Aims: Antiplatelet therapy is standard for high-risk patients like those with acute coronary syndromes or undergoing percutaneous coronary interventions. However, response to antiplatelet agents varies widely among individuals, leading to increased bleeding or thrombotic events. Platelet function testing (PFT) has been explored to guide antiplatelet therapy selection, aiming to optimize safety and efficacy outcomes. Arachidonic acid (AA) is considered the most useful agonist to evaluate aspirin efficacy, however, some papers have highlighted that using AA in PFT as an agonist is not sufficient to identify patients at risk, as multiple mechanisms are responsible for poor clinical outcomes in aspirin-treated patients (including COX-1 inhibition). This study aims to analyze platelet aggregation (PA) in patients on aspirin treatment using a standardized method to observe the different response to collagen, a

platelet agonist suitable to study aspirin action, in the entire population and in those who exhibit a lack of response to AA.
Methods: From a single center database analysis conducted on 11,913 subjects between January 1, 2004 and December 31, 2022, after exclusion of pathologies and medications able to alter the results of light transmission aggregometry (LTA), we included 3280 patients on treatment with aspirin 75-150 mg/die for at least 2 weeks. Platelet aggregation (PA) was assessed at 4 minutes using platelet agonists collagen 2 mcg/ml and AA 0.75 mM. Patients were categorized based on interquartile range (IQR) into optimal, high, or low platelet reactivity (OPR, HPR, LPR).
Results: The IQR in response to the single agonists was respectively: 20-60 for collagen, and 0-16 for AA. The medians for the same agonists were 36 (collagen) and 0 (AA). From our database we found a total of 2354 (72%) patients had complete absence of response to AA 0.75 mM. Of these 2354 patients, with absence of PA, 372 patients had PA in response to collagen >60%, a parameter that identify patients with HPR.
Conclusions: Despite high PA values in response to AA being useful for identifying patients on aspirin with HPR, a considerable proportion of those patients with absent responses to AA have still been identified as having HPR, for independent COX-1 inactivation. These results underscore the role of evaluating PA in response to collagen to identify patients undergoing aspirin treatment with HPR. Nevertheless, these patients should still be considered at risk for cardiovascular events despite their optimal response to AA. Collagen induced PA could be a useful tool for a tailored aspirin therapy.

CO083

PSYCHOLOGICAL RISK PROPENSITY AND MODIFIABLE CARDIOVASCULAR RISK FACTORS: INSIGHTS FROM THE CV-PREVITAL TRIAL

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Background and Aims: Preventing cardiovascular (CV) disease is primary for reducing global morbidity and mortality. This study aims to assess if individuals with a higher psychological risk propensity exhibit elevated modifiable CV risk factors. «Risk propensity» refers to a psychological inclination towards general risk-taking behaviour, while «CV risk» denotes the risk of developing a CV condition.
Methods: Cross-sectional analysis on 2,199 individuals (aged ≥45 y; 55.1% women, mean (standard deviation) age 57 (5) years) from the CV-PREVITAL Study (recruited at IRCCS Neuromed centre of recruitment, 2022-2024), a multicentre, prospective, randomized, controlled, open-label interventional study, sponsored by the Italian Ministry of Health, designed to compare the efficacy of an educational and motivational mobile health intervention with that of usual care in primary CV prevention. Baseline assessments included questionnaires on medical history, lifestyle, psychometrics, alongside direct measurements. The Risk Propensity Scale (RPS), a self-report psychometric questionnaire, was rated on a 9-point scale ranging from 1 (totally disagree) to 9 (totally agree), and administered to gauge individuals' general risk inclination. The Moli-sani Risk Score, a validated algorithm created from the population of the Moli-sani Study, was calculated to assess the combined impact of nine common modifiable risk factors on CV risk (smoking, diet, physical activity, obesity, LDL and HDL cholesterol, triglycerides, blood pressure, and glycated haemoglobin). For better interpretability, the Moli-sani Risk Score was standardized such that one unit of the rescaled score corresponds to the CV risk equivalent of one additional year of age at baseline. Multivariable linear or logistic regression analysis was used to test the association between CV risk factors or Moli-sani risk score (dependent variable, or continuous) and RPS (in continuous or in fifths), adjusted for age and sex.

Table 1.

Distribution of Cardiovascular Risk Factors According to Psychological Risk Propensity Score in the CV-PREVITAL Trial

	Propensity Risk Score			
	Low	Middle	High	
Variable	Q1 (N=430)	Q3 (N=451)	Q5 (N=450)	P for trend*
RPS score range	7 - 13	19 - 23	29 - 51	
RPS score median	10	21	32	
Age - mean (SEM)	59.2 (0.4)	58.1 (0.4)	57.4 (0.4)	0.0044
Men - N (%)	160 (37.2%)	220 (48.8%)	219 (48.7%)	0.0007
Cardiovascular Risk Factors				
Smokers - N (%)	49 (17.7%)	68 (22.2%)	111 (35.7%)	<0.0001
Mediterranean diet -points mean (SEM)	5.7 (0.1)	5.4 (0.1)	5.4 (0.1)	0.034
Mean arterial pressure - mmHg mean (SEM)	95.2 (0.5)	93.8 (0.5)	95.2 (0.5)	0.63
Relative Fat Mass - mean (SEM)	34.9 (0.2)	35.8 (0.2)	36.1 (0.2)	0.0004
Moderate to high physical activity - N (%)	166 (38.6%)	163 (36.1%)	155 (34.4%)	0.10
Glycated haemoglobin- (%) mean (SEM)	50.8 (0.7)	50.1 (0.7)	52.2 (0.7)	0.084
LDL cholesterol - mg/dL mean (SEM)	118 (2)	122 (2)	121 (1)	0.13
HDL cholesterol - mg/dL mean (SEM)	59.2 (0.6)	59.5 (0.6)	57.7 (0.6)	0.070
Triglycerides - mg/dL mean (SEM)	109 (3)	110 (3)	120 (3)	0.098
Moli-sani Risk Score				
MRS - mean (SEM)	-7.9 (0.3)	-7.5 (0.3)	-5.9 (0.3)	<0.0001
MRS absolute increase (%)	ref	+1.9%	+25%	

*Adjusted for age and sex. RPS means Psychological Risk Propensity Score, SEM means standard error of the mean. MRS means Moli-sani Risk Score

Results: In multivariable linear regression analysis (adjusted for age and sex), a one standard deviation (SD) increase in RPS (mean 21.2, SD 8.4) was positively associated with a 0.6 unit increase in the Moli-sani risk score (P<0.0001). The Table 1 illustrates the distribution of the Moli-sani risk score and its components according to fifths of the RPS. Participants with higher RPS were younger and more predominantly men, showing a worse CV profile for all CV risk factors, with the exception of blood pressure (Table 1). In particular, adjusted odds ratios for smoking increased with higher RPS fifths (OR=2.41, 95%CI: 1.63 to 3.56 for Q5 *vs* Q1). The Moli-

sani Risk Score increased with higher RPS scores, with individuals in Q5 having a 25% higher value compared to those in Q1 ($p<0.0001$, Table 1).
Conclusions: These findings underscore the importance of considering psychological risk propensity in CV risk assessment and the development of personalized intervention strategies. Individuals with a higher "risk propensity" may benefit from targeted interventions aimed at mitigating CV risk factors and reducing the incidence of CV disease. Further research is warranted to elucidate the mechanisms underlying these observed associations and to optimize strategies for the prevention and management of CV disease.

CO084

COMPARISON OF CARDIOVASCULAR RISK PROFILES BETWEEN SUBJECTS ENROLLED IN THE CV-PREVITAL TRIAL OR IN THE MOLI-SANI STUDY: A 15-YEAR COMPARATIVE ANALYSIS

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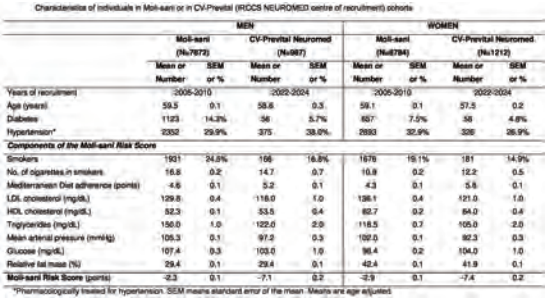
Background and Aims: The CV-PREVITAL trial, a multicentre, prospective, randomized, controlled, open-label interventional study sponsored by the Italian Ministry of Health, seeks to evaluate the efficacy of a mobile health intervention compared to standard care in reducing cardiovascular (CV) events and improving the CV profile risk. The present study aimed to compare the evolution of CV risk factors over a 15-year period between the CV-PREVITAL trial (recruited at IRCCS NEUROMED, Pozzilli) and the Moli-sani Study cohort.
Methods: At the IRCCS NEUROMED recruitment centre, 2,268 individuals older than 45 years, apparently free of cardiovascular disease were recruited from October 2022 to February 2024 to participate in the CV-PREVITAL trial. These individuals were compared for their CV risk profile at baseline with 16,656 individuals from the Moli-sani Study, age>45 years, free from CVD at baseline, recruited between 2005-2010, who formed the derivation cohort for the Moli-sani Risk Score (MRS). The MRS is a validated algorithm that assesses the impact of nine common modifiable CV risk factors on fatal or non-fatal CV events. These factors, including smoking, diet, physical activity, obesity, serum lipids, hypertension, and glycaemic profile, are continuously and by weight incorporated into the score. A higher MRS indicates a stronger modifiable CV risk. To enhance interpretability, we standardized the MRS, equating one unit of the re-scaled score with the CV risk equivalent of one additional year of age at baseline. Laboratory tests were measured using the same methods, except for glucose levels, which were assessed as glycated haemoglobin in CV-PREVITAL and then converted to mean glucose for comparison with Moli-sani data.
Results: The Table 1 presents the mean characteristics of individuals enrolled in the Moli-sani (2005-2010) or CV-Prevital (IRCCS NEUROMED centre of recruitment; 2022-2024) cohorts, separately for men and women. Mean values are adjusted for age. Nearly all CV risk factors were more favourable in the CV-Prevital cohort compared to the Moli-sani cohort, excepted for hypertension in men and glucose levels in women. The distribution of relative fat mass was similar in both populations. Notably, the mean MRS was clearly lower in the CV-Prevital cohort compared to the Moli-sani cohort (-4.8 and -4.5 point in men and women, respectively; see the Table 1), indicating an overall more favourable CV risk profile in the CV-Prevital participants.
Conclusions: The findings of this 15-year comparative analysis highlight important differences in CV risk profiles between individuals enrolled in the CV-PREVITAL trial or in the Moli-sani Study. Despite both cohorts comprising individuals without prior apparent CV disease, being recruited from the same age range and setting, participants in the CV-Prevital trial exhibited a more favourable CV risk profile, characterized by lower levels of modifiable risk factors and a significantly lower median Moli-sani Risk Score. These results might underscore the potential impact of a prevention culture diffused at regional level during the last 20 years by the Moli-sani study, in effectively reducing CV risk. Further research is warranted to elucidate the mechanisms underlying these observed differences and to optimize strategies for CV disease prevention and management.

Table 1.



Characteristics of individuals in Moli-sani or in CV-Prevital (IRCCS NEUROMED centre of recruitment) cohorts

	MEN				WOMEN			
	Moli-sani (N=7672)		CV-Prevital Neuromed (N=997)		Moli-sani (N=8784)		CV-Prevital Neuromed (N=1212)	
	Mean or Number	SEM or %	Mean or Number	SEM or %	Mean or Number	SEM or %	Mean or Number	SEM or %
Years of recruitment	2005-2010		2022-2024		2005-2010		2022-2024	
Age (years)	59.5	0.1	58.6	0.5	59.1	0.1	57.5	0.2
Diabetes	1123	14.3%	56	5.7%	657	7.5%	58	4.8%
Hypertension*	2352	29.9%	375	38.0%	2893	32.9%	326	26.9%
Components of the Moli-sani Risk Score								
Smokers	1931	24.8%	166	16.8%	1676	19.1%	181	14.9%
No. of cigarettes in smokers	16.8	0.2	14.7	0.7	10.9	0.2	12.2	0.5
Mediterranean Diet adherence (points)	4.6	0.1	5.2	0.1	4.3	0.1	5.6	0.1
LDL cholesterol (mg/dL)	129.5	0.4	118.0	1.0	136.1	0.4	121.0	1.0
HDL cholesterol (mg/dL)	52.3	0.1	53.5	0.4	62.7	0.2	64.0	0.4
Triglycerides (mg/dL)	150.0	1.0	122.0	2.0	116.5	0.7	105.0	2.0
Mean arterial pressure (mmHg)	105.3	0.1	97.2	0.3	102.0	0.1	92.3	0.3
Glucose (mg/dL)	107.4	0.3	103.0	1.0	96.4	0.2	104.0	1.0
Relative fat mass (%)	29.4	0.1	29.4	0.1	42.4	0.1	41.9	0.1
Moli-sani Risk Score (points)	-2.3	0.1	-7.1	0.2	-2.9	0.1	-7.4	0.2

*Pharmacologically treated for hypertension. SEM means standard error of the mean. Means are age adjusted.

CO085

VENOUS THROMBOEMBOLISM IN PAEDIATRIC PATIENTS: A MONOCENTRIC, OBSERVATIONAL, AND RETROSPECTIVE STUDY IN THE YEARS OF THE SARS-COV-2 PANDEMIC

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Background and Aims: Venous thromboembolism (VTE) is rare in children, although VTE is increasingly recognized as a complication of hospitalization among paediatric patients. SARS-CoV-2 infection may play a prothrombotic role even in children. The aim is to assess the clinical characteristics of hospitalized paediatric patients with VTE in the years immediately preceding and following the outbreak of the SARS-CoV-2 pandemic.
Methods: In this retrospective study, we analyzed medical records from paediatric patients (age <18 years) with a diagnosis of VTE who were hospitalized from January 1, 2018, to December 31, 2022, in the Women's and Children's Hospital of Verona, Italy.
Results: During the 5-year period 2018-2022, out of a total of 7,686 admissions were reported 51 VTE diagnoses (0.66%), of which 40 were cases of deep vein thrombosis (DVT) and 16 of superficial vein thrombosis (SVT), while 5 patients had both DVT and SVT. Almost all cases of SVT were associated with peripheral venous lines (14/16-87.5%). As regards DVT, there was a slight prevalence of male sex (24/40-60.0%). Nine events were observed in newborns (<1 month) and 6 events in infants (1 month-1 year). Most of events were represented by DVT in "classical" sites (26/40), but 8 were cerebral vein thromboses, which were mostly affecting newborns (5/8), and were 5 splanchnic vein thromboses. The presence of central venous lines was the most prevalent risk factor (17/40-42.5%). Seven patients had concomitant neoplastic disease and nine had recent surgery. Thrombophilia was irregularly investigated. Considering each single year of the 5-year period, the incidence of VTE did not show significant changes, even when comparing the years of the SARS-CoV-2 pandemic with the immediately preceding years (Figure 1). None of the recorded VTE cases was positive for SARS-CoV-2 infection.
Conclusions: These observational data do not support SARS-CoV-2 infection as a relevant VTE risk factor in hospitalized paediatric population.
Figure 1: Incidence of venous thromboembolism (VTE) in paediatric patients who were hospitalized in the Institutes of Paediatrics of University Hospital of Verona during the 5-year period 2018-2022. Data are reported including both deep vein thrombosis (DVT) and superficial vein thrombosis (SVT) – Figure 1A, n=51 – or only DVT – Figure 1B, n=40.

Figure 1.

CO086

A NEW IMEA CUT-OFF FOR THE DIAGNOSIS OF HEPARIN INDUCED THROMBOCYTOPENIA

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Background and Aims: Heparin induced thrombocytopenia (HIT) is a rare adverse effect of heparin therapy due to the production of IgG antibodies against heparin-platelet factor 4 (H-PF4) complexes. The diagnosis requires detection of antibodies against heparin/PF4 by immunological assay and HIPA test, which is technically demanding as functional test. The aim of our study was to estimate the Heparin induced Multiplate® electrode aggregation (HIMEA) cut-off for the detection of HIT positive patients.
Methods: We included 48 patients with clinical suspicion of HIT (4T score 4.8±1.6)and positivity by immunological test (CLIA),in whom we performed HIPA. In all patients we performed HIMEA test. Citrate whole blood was collected from healthy donors and incubated with patient's serum; platelet aggregation in response to unfractionated heparin(0.5U/ml-100U/ml) was evaluated. Patients were considered HIT positive by following criteria: typical sigmoid curve reflecting platelet aggregation, AUC for low-dose heparin 0.5U/mL >30U, AUC for high-dose heparin 100U/ml <50% of the low-dose heparin AUC, and AUC<30U without heparin.
Results: All patients [25M/23F; mean age:70.1±12.1] were analyzed by CLIA,(Acustar IgG,>1U/mL-median 14.43U/mL [2.27-40.06]) and then evaluated with HIPA. HIPA positive test was found in 37 samples(77.1%). In 89.2% of HIPA positive patients the 4T score was≥4.
Data from HIMEA showed that the AUC with 0.5U/mL and 100U/mL heparin were 87(42 -152)U and 34(20-49)U respectively. Patients who fulfilled all the above

mentioned criteria for a positive HIT by HIMEA were 28 out of 37 HIPA positive patients (75.7%), 9 HIPA positive patients resulted negative by HIMEA,11 patients were negative by both tests. The sensitivity and specificity resulted 71.8% (55.1-85.0%) and 100% (66.4-100%). The PPV was 100% (87.7-100%), the NPV was 45.0% (33.2-57.5%). We also calculated the% inhibition of AUC by high dose heparin [[(AUC heparin 0.5U/ml *AUC heparin 100 U/ml)/AUC heparin 0.5U/ml]*100]. The% inhibition resulted 64.0% (28.5-77.8%). Comparing these results with HIPA by ROC curve analysis, we established a cut-off of 21.5% (AUC 0.984, p<0.001). HIMEA assay with 21.5% cut-off yields sensitivity of 97.3% (85.8-99.9) and specificity of 100% (71.5-100). With 21.5% cut-off, HIMEA results were concordant with HIPA, the Cohen's kappa coefficient was 0.943, p<0.001: 36 patients had both test positive,11 both test negative, 1 patient had a discordant result (false negative).

Conclusions: Combination of immunological assay with functional test improves the accuracy of HIT, but functional test are limited to few, expert laboratories. We observed that the Multiplate® cut-off <21.5% (% inhibition of AUC by high-dose heparin) is a reasonable limit to exclude HIT in patients with HIT clinical suspicion. The combination of CLIA and HIMEA could simplify the diagnosis in suspected HIT patients.

CO087

HLA LOCI PREDISPOSING TO VITT: POTENTIAL ROLE OF THE INTERACTION BETWEEN A PF4-DERIVED PEPTIDE AND MHCII

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Background and Aims: Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare severe complication of adenoviral-vector COVID-19 vaccines for which no risk factors have been identified so far and also the higher incidence in young women initially reported seemed to disappear in later series (PMID: 37285904). Some loci of the human leukocyte antigen (HLA) system have been shown to be associated with autoimmune disorders, like thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT) and immune thrombocytopenia (ITP) (PMID: 30543580). These conditions show some similarities with VITT because they are all characterized by thrombocytopenia, are caused by immune mechanisms, and have thrombosis as a crucial clinical feature for TTP, HIT and VITT, but also associated with ITP. Aim of our study was to identify gene variants possibly associated with VITT susceptibility focusing on HLA.

Methods: Whole exome sequencing (WES) was performed in a cohort of 16 Italian patients who survived VITT, HLA typing by WES was confirmed by targeted sequencing. An in silico prediction model was applied to identify the affinity of HLA molecules for PF4-derived peptides. HLA-A, -B, -C, -DRB1, -DPB1 and -DQB1 allele frequencies were compared with those of 120926 (for HLA-A, -B, -C, -DRB1), 13099 (for -DPB1) and 25259 (for -DQB1) individuals from the Italian national Bone Marrow Donor Registry (IBMDR) (PMID: 31207125). HLA-DQA1 allele frequencies was compared with that of five smaller italian control populations reported in the allelefrequencies.net database.

Results: We identified some specific HLA class II alleles significantly more frequent in subjects who developed VITT than in a large control Italian population: DRB1*11:04 (OR 2.501, p=0.037) and DPB1*17:01 (OR 4.518, p=0.016). Also DQA1*01:01 and DQA1*05:01 allele frequency was significantly increased in VITT patients compared with five smaller control populations. Moreover, HLA class I allele B*53:05 and HLA class II allele DPB1*35:01 had an increased frequency in VITT patients compared to the control population, however this allele was found only in 1 out of 32 VITT alleles, thus these alleles were not considered statistically significant. *In silico* analysis revealed that DRB1*11:04 shows increased affinity for PF4-derived peptides, one of which (ITSLEVIKA) was a stronger binder, with a high likelihood to be presented by DRB1*11:04. This PF4-derived peptide contains two aminoacids, Glu28 (E) and Ala32 (A), present in the 8 aminoacid binding site of anti-PF4 antibodies identified in VITT patients (PMID: 35377937).

Conclusions: Our findings suggest that a genetic predisposition to an abnormal immunological response to ADV-vector vaccine administration exists. While HLA-typing of candidates to Ad vector vaccines is probably unfeasible, our results may instead be considered to prevent thrombotic complications related to the use of adenoviral vector platforms for gene therapies. Future studies in larger cohorts are warranted to further confirm the relationship between HLA and VITT and to explore if anti-PF4 antibody levels are associated with the identified class II HLA alleles.

Acknowledgements: The contribution of S. Sorrentino[3], M. Scavone[4], M. Marchetti[5], L. Barcella[5], S. Basili[6], L. Contino[8], A. Rogolino[11], R. Curcio[16] for patient enrollment.

CO088

FLOW CYTOMETRY EXPRESSION OF P-SELECTIN AS A FUNCTIONAL ASSAY FOR THE DIAGNOSIS OF HEPARIN-INDUCED THROMBOCYTOPENIA

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Background and Aim: Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin therapy, caused by antibodies against platelet factor 4 (PF4)/heparin complexes. HIT diagnosis requires both the demonstration of the presence of anti-PF4/heparin anitbodies (immunological test) and that they are functionally active against platelets (functional test). Gold standard functional tests (HIPA, platelet serotonin release) require the use of washed platelets and of several donors of control platelets, for the variability of normal platelet response to anti-PF4/heparin antibodies. Flow cytometry (FC) functional test detects the expression of p-selectin on control platelet rich plasma (PRP) upon exposure to anti-PF4/heparin antibodies. The aim of our study is to demonstrate that FC is a sensitive method able to detect platelet activation in virtually all the donor platelets.

Methods: Whole blood (WB) samples of healthy donors, collected in NaCitrate containing tubes, were provided by the Transfusion Center of A. Gemelli Hospital IRCSS. We evaluated 16 HIT positive plasma samples previously analyzed in chemiluminescence with HemosIL Acustar HIT IgG assay (cut-off values were <1 U/mL). The FC assay was performed according as follows: WB samples were centrifuged at 650 rpm x 15 min to obtain PRP. PRP was incubated for 1 h in different conditions: (1) PRP+ HIT plasma+buffer; (2) PRP+ HIT plasma+heparin 0.3 IU/mL; (3) PRP+ HIT plasma+heparin 100 IU/mL; (4) PRP+ control platelet-poor plasma (PPP)+ thrombin receptor-activating peptide (TRAP) 10 uMol/L as positive control and (5) PRP+ control PPP+ buffer as negative control. An aliquot of the reaction mixture was incubated with CD42b monoclonal antibody (mAb) for platelet identification and CD62P (p-selectin) mAb and analyzed by a flow cytometer Cytoflex 500. Mean fluorescence intensity (MFI) was measured. Each HIT sample was tested by using two PRPs from two different healthy donors.

Results: FC measurement of p-selectin (CD62p) exposure showed a typical laboratory HIT pattern characterized by heparin-dependent platelet activation with heparin 0.3 IU/mL, abolished by high heparin dose (100 IU/mL). This pattern was confirmed for all 16 HIT positive samples, each of whom was tested with PRPs obtained from two healthy donors, for a total of 32 healthy donors tested (Table 1).

Conclusions: Flow cytometry measurement of p-selectin expression can be used for the confirmation of HIT. Our data suggested that the accuracy and sensitivity of the FC method allows the use a single healthy donor PRP, making this assay less time consuming and accessible to many laboratories.

Table 1.

Sample	HemosIL Acustar HIT IgG assay cut-off <1 U/mL	Flow Cytometry Assay Donor #1	Flow Cytometry Assay Donor #2
#1	19,44	POSITIVE	POSITIVE
#2	1,51	POSITIVE	POSITIVE
#3	1,16	POSITIVE	POSITIVE
#4	12,48	POSITIVE	POSITIVE
#5	8,69	POSITIVE	POSITIVE
#6	6,85	POSITIVE	POSITIVE
#7	>128	POSITIVE	POSITIVE
#8	57,29	POSITIVE	POSITIVE
#9	13,09	POSITIVE	POSITIVE
#10	25,25	POSITIVE	POSITIVE
#11	13,68	POSITIVE	POSITIVE
#12	10,63	POSITIVE	POSITIVE
#13	11,09	POSITIVE	POSITIVE
#14	8,68	POSITIVE	POSITIVE
#15	>128	POSITIVE	POSITIVE
#16	>128	POSITIVE	POSITIVE

CO089

WHOLE EXOME SEQUENCING IN VACCINE-INDUCED THROMBOTIC THROMBOCYTOPENIA (VITT)

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Background and Aims: In February 2021, few cases of unusual, severe thrombotic events associated with thrombocytopenia reported after vaccination with ChAdOx1 nCoV-19 (Vaxzevrya) or with Johnson&Johnson's Janssen vaccine raises concern about safety. The vaccine-induced thrombotic thrombocytopenia (VITT) has been related to the presence of platelet-activating antibodies directed against platelet factor 4. We investigated VITT subjects genetic background by a high-throughput whole exome sequencing approach in order to investigate VITT genetic predisposition.

Methods: Six patients (females of Caucasian origin with

a mean age of 64 years) referred to the Atherothrombotic Diseases Center (Department of Experimental and Clinical Medicine, Azienda Ospedaliero-Universitaria Careggi, Florence) with a diagnosis of definite VITT underwent Whole Exome Sequencing (WES) analysis. WES analysis was performed on Illumina NextSeq500 platform.
Results: WES analysis revealed a total of 140,563 genetic variants. Due to VITT rare occurrence, we focused attention on rare variants. The global analysis of all high-quality rare variants did not reveal a significant enrichment of mutated genes in biological/functional pathways common to patients analysed. Afterwards, we focused on rare variants in genes associated with blood coagulation and fibrinolysis, platelet activation and aggregation, integrin-mediated signalling pathway as well as autoimmune thrombocytopenia. According to ACMG criteria, 31/112 (27.7%) rare variants were classified as uncertain significance variants (VUS), whereas remaining were likely benign/benign.
Conclusions: WES analysis identifies rare variants possibly favouring the prothrombotic state triggered by the exposure to vaccine. Functional studies and/or extension to a larger number of patients might allow a more comprehensive definition of these molecular pathways.

CO090

HEPARIN INDUCED THROMBOCYTOPENIA AFTER CARDIAC SURGERY. A SINGLE-CENTER, CROSS-SECTIONAL STUDY

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Background: Cardiac surgery is a high risk setting for heparin induced thrombocytopenia (HIT). However, large differences in its incidence, rate of thrombotic complications and mortality have been reported in this context. Few studies address the pharmacological management of HIT specifically in this setting.
Objective:To analyze the diagnostic issues, incidence, outcomes, and management of HIT.
Methods: A retrospective observational study was conducted over a period of 10 years and 6 months on 13178 cardiac operations in a single high-volume cardiac surgery center.
Results: HIT was diagnosed in 0.22% of patients. Associated thromboembolic complications (HITT) occurred in 0.04% of cases. The type of surgery did not affect the incidence of HIT. The 4T score showed a 99.9% negative predictive value. The chemiluminescence IgG test positivity rate was highly predictive of HIT. Two deaths at 30 days were registered, and both in patients with associated thrombosis. The mortality rate was 6.9% in HIT and 33.3% in HITT patients. Heparin was discontinued in all patients, and fondaparinux was the most used alternative anticoagulant. Warfarin was often started early after surgery, and although it was rarely stopped when the diagnosis of HIT was made, no new thromboembolic complications subsequently occurred.
Conclusions: Although rare, HIT is characterized by a high mortality rate in this setting, especially if thrombotic complications occur. Large multi-centric studies or an international registry should be created to enhance the scientific evidence on HIT diagnosis and management in this context.

CO091

INFLUENCE OF GENOTYPE CHARACTERISATION FOR PHENOTYPES PROFILING IN PROTEIN S DEFICIENCY

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Background and Aims: Among patients with protein S deficiency it has been shown that the lower the protein level, the greater is the odd of thrombotic events. To date, more than 300 PROS1 genetic variants have been reported. To investigate mutations in Protein S-deficient patients with thrombosis to explore genotype/phenotype correlation.
Methods: Free protein S levels were obtained by a turbidimetric method and genetic investigations carried out using Sanger/Next-Generation-Sequencing. Novel mutations were interpreted according to ACMG guidelines. mRNA was isolated to obtain cDNA and used for direct sequencing.
Results: We investigated 15 probands and their relatives with a confirmed protein S deficiency (Table 1). Median age at observation was 46 years (IQR: 32.0;65.0), mostly women (8, 61.5%). They suffered mainly from pulmonary embolism (n= 3, one case observed in the postpartum period). Notably, two members of the same family (a young man and his mother were diagnosed with a splanchnic and cerebral thrombosis, respectively). As for genetics, seven novel variants with a possible deleterious effect (ACMG guidelines) were identified. The in-frame c.346+3A>TA variant, causing a skipping of PROS1 exon 4, had a significant impact on the protein.

Among the remaining six variants, one was observed in a splicing site (#1), three were in an already known mutational site (# 6, 11, 12). The variant described in the #12 determines an unstable protein. One further mutation was in the promoter region and one was an in-frame deletion in the exon 12 likely causing a shorter protein (#7). The #13 with juvenile stroke carried the previously described p.Pro626= variant, already demonstrated to influences mRNA maturation. Mutations impacting on glycosylation (#9), causing deletion (#7) or an unstable protein (#12) are associated with the lowest protein circulating levels.

Conclusions: PROS1 investigation can be helpful in predicting protein S plasma levels and possibly clinical phenotype.

Table 1.

Clinical and laboratory information

Patients	Age at the observation (years)	Free protein S levels (%)	Clinical information	Nucleotide change	cDNA change	Known (K) or Novel (N) variant	Damaging effects/ ACMG-based pathogenicity evidence
#1£	74	33.0	Recurrent lower limb VT	c.79+5G>A	NA	N	Likely pathogenic
#2£	61	36.5	Pulmonary embolism	c.200A>C	p.Glu67Ala	K (Borrello, K et al. Blood 1986)	Loss of APC cofactor activity
#3	63	42.6	Recurrent VT	c.121C>A	p.Arg41Ser	K (Klaus Orso, M et al. Thromb Haemost 2016)	Retained propeptide
#4*	29	23.0	Pulmonary embolism	c.1574C>T	p.Ala525Val	K (Tangeli, P et al. Thromb Res 2021)	Enhanced intracellular protein S degradation
#5	27	43.0	Asymptomatic	c.-168G>T	NA	N	Likely pathogenic
#6	43	48.0	Pulmonary embolism	c.1009G>A	p.Gly337Arg	N	Likely pathogenic
#7	40	12.0	Lower limb VT	c.1632_1638del	p.Met611_Ala613	N	Pathogenic
#8	33	27.6	Familial VT	c.1037G>A	p.Gly336Asp	K (Ngan, E et al. Hum Mut 2009)	Likely pathogenic
#9	8	12.0	Lower limb VT at the age of 5 years	c.1681T>C	p.Ser561Pro^ Heerlen variant	K (Ferrie KW et al. Blood 1995)	Ablation of the 499 N-glycosilation site
#10§	31	27.0	Splanchnic VT	c.346+3A>TA	NA	N	Pathogenic
#11	45	35.0	Asymptomatic	c.785G>T	p.Gly262Val	N	Uncertain significance
#12	17	18.2	Familial VT in young relatives	c.1574C>A	p.Ala525Asp	N	Likely pathogenic
#13°	24	26.3	Familial stroke and VT	c.	p.Pro626=	K (Middeldorp, M et al. Thromb Res 2021)	mRNA aberrant maturation
#14§	29	53.0	Personal and familial VT	c.566G>T	p.Gly189Asp	K (Ahmed Abdu, M et al. JTH 2018)	Potential impact on APC cofactor activity
#15	48	38.6	Lower limb VT	c.1324-3T>G	NA	K (Beauchamp, NJ et al. Blood 2004)	Aberrant splicing

Legend to the Table 1.
We highlight strucutural/functional effects and ACMG classification as to previously described and unknown variants, respectively;
£ three asymptomatic relatives carried the mutation;
ç her son carried the p.Glu67Ala and was diagnosed with a lower limb VT;
* two additional asymptomatic relatives carried the mutation;
^ Heerlen Variant;
$ proband's mother carried c.346+3A>TA and was diagnosed with a cerebral vein thrombosis under oral contraceptive;
° one additional carrier relative with VT;
§ one relative carried the mutation and showed VT.

CO092

RESULTS FROM THE HYPOPLASMINOGENEMIA INTERNATIONAL RETROSPECTIVE AND PROSPECTIVE COHORT STUDY (HISTORY) ON PLASMINOGEN DEFICIENCY

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Background and Aims: Plasminogen (PLG) deficiency (PLGD) is an ultra-rare inherited chronic disorder that affects ~1.6 per million population. Extravascular fibrin-rich pseudomembranes accumulate on mucous membranes causing intermittent or continuous clinical manifestations including eyes, oral cavity, middle ears, respiratory, genitourinary and gastrointestinal tracts and central nervous system. PLGD clinical manifestations are not predicted by specific genetic defects or PLG levels (except for PLG activity <5%) and no severity categories are established. In addition, data guiding management of PLGD is scarce and based on case reports/series and small clinical trials. With this as background, an international observational cross- sectional study was started to create HISTORY, the first comprehensive retrospective/prospective registry to document and evaluate PLG deficiency unmet needs. The analysis of data coming from HISTORY may help to increase understanding what are the main features of PLGD, to define its natural history and to predict its course to guide the treatment.

Methods: Proband and first-degree relatives are included in the study. Clinical symptom data are collected retrospectively for at least 1-year prior study-entry and 3 years prospectively. Plasma and DNA samples are collected and processed for PLG activity, antigen level and molecular characterization. Descriptive statistics are stratified by genotype. PLG activity, antigen and age at symptom onset are reported as medians and minimum/maximum. Symptoms are reported as absolute frequencies and percentages.

Results: Currently, 160 total subjects (69 probands) have been registered by 20 International centers (9 countries). Current analysis was performed on 79 subjects genetically characterized. PLG activity, antigen levels and distribution of main clinical symptoms are reported in the Table 1.

Conclusions: Ligneous conjunctivitis, ligneous gingivitis, ear infection and vaginal lesions were the most frequent symptoms particularly in homozygotes and double heterozygotes. The HISTORY cohort is large and hopes to address unanswered questions in PLGD. Ongoing enrollment and data collection will contribute important insights to disease manifestation triggers and support the development of severity categories to predict disease course and guide treatment.

Table 1.

The analysis was performed on data collected retrospectively. PLG antigen and activity levels (values below the lowest level of detection assay, were represented as half of the lowest detection limit) and distribution of main clinical symptoms (thought to be most relevant to PLG deficiency) in homozygous/compound heterozygous, heterozygous and wild-type subjects, are reported. No MALE GENITAL SYSTEM symptoms were registered.

	Homozygote/Compound	Heterozygote	Wild-type
Number of patients	34 (20 women)	35 (18 women)	10 (7 women)
PLGAC (IU/ml) nr 80 – 132% Median [Min, Max]	14.0 [1.00, 31.0]	58.0 [41.0, 84.0]	101 [78.0, 138]
PLGAg (µg/ml) nr 70 – 215µg/mL Median [Min, Max]	16.8 [6, 54.3]	75 [38.5, 121]	105 [79.8, 247]
EYES symptoms, number of pts	10/34 (29%)	4/35 (11%)	0
Age at onset [years] Median [Min, Max]	1 [0, 65]	9.8 [3, 20]	–
Recurrent conjunctivitis	12/30 (40%)	4/4	0
Ligneous conjunctivitis (1-3 episodes)	27/30 (90%)	0	0
Other eye complications (glaucoma, mucous discharge, bacterial conjunctivitis, eyes swelling, corneal scarring, vision impairment, amblyopia, strabismus, dried secretions, chalazion, discharge and mild ptosis)	7/30 (23%)	2/4 (50%)	0
EARS symptoms, number of pts	13/34 (38%)	12/35 (34%)	2/10 (20%)
Age at onset [years] Median [Min, Max]	1 [0, 50], nas1	5 [0, 20], nas1	0.5 [0, 1]
Recurrent ear infections (1-3 episodes)	13/13	10/12 (83%)	2/2 (100%)
Other ear complications (mastoiditis, significant opacification of mastoid air cells, hearing impairment, drum perforation after trauma, otitis media)	2/13 (15%)	3/12 (25%)	0
OROPHARYNGEAL/NASAL symptoms, number of pts	17/34 (50%)	2/35 (6%)	1/10 (10%)
Age at onset [years] Median [Min, Max]	15 [3, 48]	13 [5, 21]	39
Ligneous gingivitis (1-6 episodes)	10/17 (59%)	0	0
Nasal ligneous lesions	2/17 (12%)	0	0
Loss of teeth	4/17 (24%)	0	0
Other oropharyngeal/nasal complication (cavities, lesion on the gum, periodontitis, poor hygiene without fluoride, receding gums, thin root dentin, tooth enabled back)	4/17 (24%)	2/2	1/1
RESPIRATORY symptoms, number of pts	11/34 (33%)	5/35 (14%)	1/10 (10%)
Age at onset [years] Median [Min, Max]	3.5 [1, 50], nas1	15 [4, 41], nas1	9
Episodes of hoarseness/loss of voice (1-2 episodes)	8/11 (73%)	0	0
Chronic lung disease	4/11 (36%)	0	0
Chronic cough	3/11 (27%)	0	1/1
Other oropharyngeal/nasal complication (asthma, collapsed lung, pneumonia, COPD)	7/11 (64%)	1/5 (20%)	0
GASTROINTESTINAL TRACT symptoms, number of pts	6/34 (18%)	2/35 (6%)	1/10 (10%)
Age at onset [years] Median [Min, Max]	6 [2, 18]	19.5 [0, 39]	5
Gastric/Rectal ulcers	3/6 (50%)	0	0
Other GI complication (constipation, celiac's disease, GERD, intestinal infection, esophageal reflux, bowel pain during pregnancy, irritable bowel syndrome, reflux as an infant, diverticulosis)	5/6 (83%)	2/2	1/1
RENAL symptoms, number of pts	4/34 (12%)	0	1/10 (10%)
Age at onset [years] Median [Min, Max]	13 [5, 28]	–	23
Hematuria/Microalbuminuria/Renal stones	4/4	0	1/1
CARDIOVASCULAR symptoms, number of pts	4/34 (12%)	7/35 (20%)	0
Age at onset [years] Median [Min, Max]	30 [6, 50]	36 [0, 53]	–
Hypertension	3/4 (75%)	5/7 (71%)	0
Other cardiovascular symptoms (CAD, sinus tachycardia, heart murmur at birth, serology of Fallot)	1/4 (25%)	2/7 (28.5%)	0
FEMALE GENITAL SYSTEM symptoms, number of pts	12/20 (60%)	4/18 (22%)	1/7 (43%)
Age at onset [years] Median [Min, Max]	14 [9, 40]	14 [13, 16]	14 [11, 26]
Dysmenorrhea/ Menometrorragia	8/12 (60%)	4/4 (100%)	3 (100%)
Vaginal/ Cervical lesions	7/12 (58%)	0	0
Cervical polyps, Agenesis Vulvovaginal, Occlusion of fallopian tubes	2/12 (17%)	0	0
CNS symptoms, number of pts	4/34 (12%)	1/35 (3%)	1/10 (10%)
Age at onset [years] Median [Min, Max]	0 [0, 0]	11	–
Congenital occlusive hydrocephalus	4/4	0	0
Seizure	1/4 (25%)	0	0
Other CNS complications (abnormal bone growth of skull, intractable headache, ADHD, diplopia, fatigue, memory loss, other mixed anxiety disorders, sleep apnea, speech delay, tremor in hands)	0	1/1	1/1

CO093

WHOLE EXOME SEQUENCING IN FAMILIES WITH UNEXPLAINED TENDENCY FOR THROMBOPHILIA OR THROMBOANGIITIS OBLITERANS: MULTICOMPONENT ANALYSIS OF LOW FREQUENCY VARIANTS

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† in memory of Armando D'Angelo.

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Background and Aims: Whole exome sequencing (WES) may favor detection in "non classical" genes of low-frequency variants conferring genetic susceptibility to venous thrombosis (VT) and to VT-associated thromboangiitis obliterans (TAO).

Methods: WES analysis was conducted in i) *Family 1*, with two members affected by spontaneous VTE and one by trauma provoked VTE (18 years), by filtering for minor allele frequency (MAF) <4% in 192 VTE candidate genes and ii) *Family 2*, with one member affected by migrating femoral-popliteal thrombophlebitis and artery thrombosis episodes followed by ulcerations, which led to a below-knee amputation (29 years). In addition to the 192 candidates, filtering for low frequency variants was conducted in genes previously suggested by genomic and transcriptomic studies in TAO patients. Functional prediction by multi-component bioinformatics tools was implemented by database/literature search, including ClinVar annotation, quantitative trait loci (QTL) analysis and protein interactions (STRING database).

Results: Family 1. Twelve missense heterozygous variants were prioritized in patients, three of which present in all affected family members (*CRP* Leu61Pro, MAF=6.9 x 10-6; *F2* Asn514Lys, MAF=0.0002 and *NQO1* Arg139Trp, MAF=0.03). Combination of prioritized variants highlighted six proteins in two different interaction patterns (CRP - F2 - SERPINA1 - THBS1 / CRP - F2 - PLAT - VWF), supported by high score evidences. Family 2. Among the 192 VTE candidate genes, four heterozygous missense variants (*IL13* Leu72Pro, MAF=0.0001; *KLK13* His109Tyr, MAF=0.02; *PEAR1* Arg885Cys, MAF=2.9 x 10-5 and the novel *PTGIR* Tyr144Asn) were indicated as "deleterious" by protein prediction tools. The *F2* Gly271 synonymous variant, MAF=0.0086, was predicted to induce exon skipping. The propositus was homozygous for the *NOS3* Glu298, a frequent condition in TAO patients. Analysis of genes (n=81) encoding the mRNAs differentially expressed in blood from TAO patients, revealed the in linkage heterozygous variants Gly13890Ala (MAF=0.0003) and Gln24857His (MAF=0.0056), predicted as "deleterious" for Titin (*TTN*), potentially involved in endothelial cell activation.

Conclusions: This multicomponent analysis in wide groups of candidate genes provided the following evidences: i) in *Family 1*, different combinations of six missense variants, which may contribute to VTE susceptibility, highlight protein interactions, particularly in the "acute phase" biological process; ii) in *Family 2*, five potentially dysfunctional variants in the VTE candidate genes/proteins did not provide evidence for significant interaction patterns. However, three of them (F2, PEAR1 and PTGIR) have been associated with platelet phenotypes, and two (IL13 and KLK13) involved in inflammatory pathways, of noticeable interest for TAO. The inheritance patterns/features of candidate gene variants may support further genome-wide analysis to reveal still unknown genetic components.

Gene names:

CRP, C-Reactive Protein
F2, prothrombin
IL13, interleukin 13
KLK13, Kallikrein Related Peptidase 13
NOS3, Nitric Oxide Synthase 3
NQO1, NAD(P)H Quinone Dehydrogenase 1
PEAR1, platelet endothelial aggregation receptor1
PLAT, Plasminogen Activator, Tissue Type

PTGIR, prostaglandin I2 receptor
SERPINA1, Alpha-1 antitrypsin
THBS1, Thrombospondin 1
TTN, titin
VWF, Von Willebrand Factor

CO094

A NOVEL *SERPINC1* GENE MUTATION IN A COHORT OF 15 PATIENTS WITH ANTITHROMBIN DEFICIENCY

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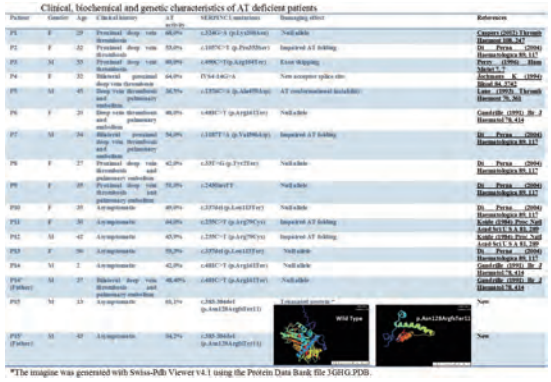
Background and Aims: Antithrombin (AT) is a hepatic protein of 464 residues encoded by the *SERPINC1* gene. The AT inherited deficiency is a rare autosomal dominant thrombophilia associated with an increased risk of venous thromboembolism (VTE) with an absolute risk of 2.3/1,000 per person-years. Its prevalence in general population is 1-5/10,000. There are two types of AT deficiency: quantitative (type I) and qualitative deficiency (type II), the first one is associated with a more severe clinical phenotype. We describe a cohort of patients with AT inherited deficiency, observed between 2004 and 2024 at the Thrombosis and Hemostasis Unit of our Institute.
Methods: We collected clinical and biochemical data of a cohort of 15 Caucasian subjects consecutively referred to us from 2008 to 2024 (Table 1). AT activity was quantitatively determined using a chromogenic factor Xa-based assay (INNOVANCE® Antithrombin); reference values in our general population range from 75- 125%. Genetic analysis of the SERPINC1 gene was performed with next-generation sequencing (NGS) with a Sure Select panel on the Miseq platform and confirmed with Sanger Sequencing. Molecular images were generated using PyMOL.
Results: Four patients suffered from isolated deep vein thrombosis (DVT; median AT activity 62%), five from DVT+ pulmonary embolism (PE, median AT activity 48%), and six were asymptomatic (median AT activity 52%). Consistent with the reported general distribution of the known AT mutations, we observed missense, null-allele, small insertions/deletions, and splicing mutations in 42%, 33%, 17%, and 8% of our patients, respectively. All but one showed one out of already known *SERPINC1* mutations (Table 1). Furthermore, we found in two asymptomatic relatives (a child and his father of 13 and 43 yrs, respectively) a novel frameshift mutation c.383-384del (p.Asn128ArgfsTer11), causing loss of glycosylation site and premature stop codon. All patients with DVT(n=4) carried previously reported mutations AT deficiency type I. Among them, two (P1, P2) had missense mutations p.Lys208Asn affecting mRNA splicing and p.Pro353Ser impairing the AT folding, respectively. Two remaining (P3, P4) carried a null-allele and a splicing mutation, respectively. Among the five patients with DVT and PE, only P5 showed the missense mutation Ala459Asp reported in AT deficiency type II leading to AT conformational instability. Four other patients presented mutations previously reported in AT deficiency type I. P6, P8 and P9 had known mutations leading to null-allele (Table 1). P7 had a missense mutation in a protein reactive site impairing the correct AT folding. Furthermore, we found known mutations in five asymptomatic subjects. Among them, three (P10, P13, P14) carried mutations leading to known null-allele already reported in AT deficiency type I. Notably, P14 (a child aged 2 yrs) was the son of a man with DVT and PE; both carried the p.Arg161Ter. The other two asymptomatic patients (P11, P12) showed the missense mutation p.Arg79Cys described in AT deficiency type II. The variant leads to an impairment of correct folding in the AT heparin binding site.
Conclusions: These data support the concept that a molecular study is helpful in characterizing patients. In rare diseases, as AT deficiency, the identification of mutations (already known as well as novel ones) allows a better correlation genotype-phenotype and in turn to tailor the clinical follow-up.

Table 1.


Clinical, biochemical and genetic characteristics of AT deficient patients

CO095

TRANSCRIPTOME STUDY IN ACUTE ISCHEMIC STROKE PATIENTS

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Background and Aims: Acute ischemic stroke (AIS) is a cerebrovascular disease leading to death and disability. The rapid restoration of cerebral blood flow includes a combination of intravenous recombinant tissue-Plasminogen Activator treatment and/or mechanical thrombectomy. Recent advancements in omics technologies suggest relevant information into clot composition, stroke mechanisms and etiology. The main goal of the study is to delve genetic aspect of AIS through the application of transcriptomic approaches. Our focus centers on the exploration of molecular signatures within cerebral thrombi (CT) and venous peripheral blood (PB) to unveil the intricate interplay between gene expression patterns and the nuanced phenotypic differences that characterize stroke etiology.
Methods: The transcriptomic profiles from CT and PB from 92 ischemic stroke patients were analyzed with Affymetrix technology by using the GeneChip Human Transcriptome Array 2.0, allowing the analysis of 44,699 genes, >285,000 full-length transcripts coverage, followed by a Gene Ontology (GO) and Reactome enrichment analysis to identify biological processes and pathways affected by different stroke etiologies. Olso, we performed a Cibersort analysis, to estimate the abundances of most common cells of the immune system in our samples.
Results: Analysis of CT data unveiled significant differences (p-value<0.05 and FoldChange=2 as threshold) in gene expression profiles when comparing strokes of LAA origin with CE and cryptogenic strokes. Notably, LAA strokes exhibited overexpression of 301 genes compared to CE strokes, with differential expression of 209 genes compared to cryptogenic strokes. GO and REACTOME enrichment analysis, showed, respectively, that biological processes such as neutrophil degranulation, regulation of cytokine production, and processes involved in damage response appear to be significantly enriched. Genes such as S100A12, S100A9 and S100A8, associated with inflammation and atherosclerotic plaque instability, were overexpressed in LAA strokes. Additionally, genes involved in inflammation, including MMP9, IL-1β and VNN2, showed significant upregulation. Concerning microRNAs (miRNAs), we highlighted the substantial overexpression of miRNA-223 in atherosclerotic-origin strokes. This particular miRNA has a significant role in inflammatory processes and has been linked, based on existing literature, to cardiovascular diseases. We found no significant differences in gene expression were detected in comparisons beyond other subtypes in CT and PB samples, emphasizing the necessity for a nuanced understanding of the underlying biology. The Cibersort analysis, highlights a robust activation of the immune response in the aftermath of the ischemic event suggesting a similar immune cell composition in both CT and PB, specifically, a predominance of neutrophil, constituting 33% and 66% of the total, respectively.
Conclusions: Transcriptome profiling has provided valuable insights into the molecular landscape of AIS.The overexpression of genes such as MMP-9, S100A12, S100A9 and S100A8 in atherosclerotic strokes underscores their association with plaque instability and adverse neurological outcomes. Dysregulation of genes such as IL-1β exacerbates ischemic injury, highlighting their crucial role in AIS pathophysiology. Transcriptome signatures hold promise in distinguishing between stroke etiologies, paving the way for personalized approaches to secondary stroke prevention.

CO096

GENETIC PROFILING OF PATIENTS WITH UNPROVOKED VENOUS THROMBOEMBOLISM: INSIGHTS FROM NEXT-GENERATION SEQUENCING ANALYSIS

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Background and Aims: Some patients who have experienced unprovoked venous thromboembolism (VTE) may have a genetic predisposition without any known inherited thrombophilia. In such cases, there might be unidentified genetic mutations, or a complex genetic architecture involving multiple genetic candidates instead of a single defect. This study aims to use Next-Generation Sequencing (NGS) as a valuable tool to reveal new mutations and potential interactions among multiple genetic factors contributing to the thrombotic phenotype in this subset of patients.
Methods: Consecutive patients negative for known inherited thrombophilia and with a history of unprovoked VTE at a young age (range 18-45 years) with or without a strong family history of VTE, underwent genetic analysis of 33 relevant coagulation genes using NGS. DNA extracted samples were sequenced by targeted capture NGS, using a custom panel of biotynylated oligonucleotides (xGenTM Hyb Panel, Integrated DNA Technologies, Los Angeles, CA, USA) consists of 861 probes covering coding regions and flanking exon/intron boundaries of 12 PA putative genes (A2MC, CPB2, F2, F3, F5, F7, F8, F9, F10, F11, F12, F13A1, F13B, FGA, FGB, FGG, KLKB1, KNG1, PLAT, PLG, PROC, PROCR, PROS1, PROZ, SERPINA5, SERPINA10, SERPINC1, SERPIND1, SERPINE1, SERPINF2, THBD, TFPI, VWF). Captured libraries were sequenced using NextSeq550 (Illumina) platform, while bioinformatic analysis was performed using bioinformatic tools (CLC genomics Workbench, Qiagen).
Results: A group of 60 unrelated patients, consisting of 31 males and 29 females with an average age of 37 years (range 18-73), were enrolled. Among them, 38 (63.3%) had a significant family history of VTE. Overall, 250 genetic variants were detected. Each patient carried out 64 genetic variants on average (range 48-89). The main

findings are reported in Table 1. Interestingly, we found eleven patients with the same multiple nucleotide variant (MNV) on SERPIN A5, 9 heterozygous and 2 homozygous, while 3 other MN*Vs* were heterozygous variants on F5, F13B and PROZ, respectively. Instead, 236 variants (94.4%) were Single-Nucleotide Variants (SNVs) of which 126 were non-synonymous. Among them, 25 SN*Vs* were not recorded in any database, while in 37 patients we found SN*Vs* already classified as pathogenic (1), likely pathogenic (10), unknown significance (VUS)(10).

Conclusions: We have conducted a comprehensive analysis of the NGS data of a customized gene panel and have found several genetic variants whose effects are uncertain. These variants may have an impact both on prothrombotic and prohemorrhagic pathways, and may even have opposing effects. Some of these mutations may be deleterious and linked to VTE, while others may modify the effects of pathogenic mutations on clinical expression. Currently, we are performing protein functionality assays to determine how these mutations affect the function of procoagulant or anticoagulant protein, and thus correlate these findings with the clinical phenotype.

Table 1.

Gene	Total number of variants	Synonymous	Non-synonymous	Predicted effect (likely pathogenic, VUS or pathogenic)	Patient code carring variants with already predicted effect (likely pathogenic, VUS e pathogenic)
A2M	7	4	3	/	/
CPB2	7	5	2	/	/
F10	5	4	1	1	S31
F11	8	7	1	/	/
F12	4	2	2	/	/
F13A1	8	2	6	/	/
F13B	6	3	3	1	S4, S50
F2	7	3	4	2	S15 S72
F3	2	1	1	/	/
F5	35	16	19	/	/
F7	3	1	2	/	/
F8	5	3	2	/	/
F9	2	1	1	/	/
FGA	3	1	2	1	S5
FGB	7	2	5	2	S1, S7
FGG	2	2	0	/	/
KLKB1	4	0	4	/	/
KNG1	13	6	7	/	/
PLAT	6	3	3	/	/
PLG	17	12	5	/	/
PROC	8	6	2	2	S7, S32
PROCR	4	3	1	/	/
PROS1	6	2	4	2	S8, S101; S9
PROZ	4	2	2	/	/
SERPIN A10	7	1	6	1	S49
SERPIN A5	9	3	6	/	/
SERPIN C1	6	3	3	1	S6
SERPIN D1	4	3	1	/	/
SERPIN E1	3	1	2	/	/
SERPIN F2	5	2	3	/	/
TFPI	4	1	3	1	S16, S18
THBD	3	0	3	1	S10
VWF	36	19	17	6	S7, S8(2), S11, S12,S13, S25, S34(2), S41, S44, S48, S51, S54(2), S56, S72
Total	250	124	126	21	

Main findings of the genetic variants detected in the population study.

CO097

EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS AT REDUCED DOSE IN PATIENTS WITH SEVERE HEREDITARY THROMBOPHILIA

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Background and Aims: It has already been showed that direct oral anticoagulants (DOACS) are effective and safe for the treatment of venous thromboembolism (VTE) in patients with hereditary thrombophilia, even severe. However, the efficacy of DOACS at reduced doses for the secondary VTE prevention is still controversial in patients with severe hereditary thrombophilia. The aim of this prospective cohort study is to evaluate the rate of recurrent VTE and bleeding complications in patients with severe inherited thrombophilia treated with DOACs at reduce doses for the secondary prevention of VTE.

Methods: We enrolled all consecutive adult patients with a diagnosis of previous VTE referred to our Centre between January 2014 and December 2021, identified as carries of severe hereditary thrombophilia, treated with full dose anticoagulant therapy for at least 3 months who subsequently underwent treatment with reduced doses of DOACS for at least 3 months. Deficiency of protein S (PS), protein C (PC), or antithrombin (AT), homozygosity for factor V Leiden (FVL) or prothrombin mutation (PTM), and combined thrombophilia were considered as severe thrombophilia. Outcomes of the study were incidence rates of symptomatic recurrent VTE and bleeding complications during reduced regimen DOACS anticoagulation. The hazard ratios (HRs) and 95% CI for the time to development of recurrent VTE or bleeding were estimated using the Cox proportional hazard model and adjusted for type of thrombophilia, duration of anticoagulation and type of DOACs.

Results: We enrolled 192 patients with severe thrombophilia (mean age 57.5 years, M 48.5%). 45 (23%) had PC deficiency, 61 (32%) PS deficiency, 29 (15%) AT deficiency, 18 (9%) homozygous FVL, 3 (2%) homozygous PTM, 27 (14%) combined heterozygosity, and 9 (5%) FV pseudo-homozygosity. Mean duration of full anticoagulation was 6.3 months. Among this cohort, 71 (36%) continued full-dose anticoagulation, 79 (41%) stopped anticoagulation after a period of DOACs at reduced doses, 42 (23%) are currently undergoing anticoagulant therapy with DOACs at a reduced dose (18 with rivaroxaban 10 mg and 24 with apixaban 2.5 mg BID). The cumulative incidence of VTE recurrence in patients who continued reduced dose DOACS was 4.7% (95%CI, 5.5-17.2) (median follow-up time 20 months [10-24]) *vs.* 15% (95% CI, 7.8–26.5%) in patients who stopped anticoagulation [HR 0.26 (95%CI 0.058-1.17, p 0.07)] (median follow-up 13 months [6-26]) and 1.4% (95%CI 0.036-7.8%) in patients who continued full-dose anticoagulation (median follow-up 36 months [6-48]) [0.12 (95%CI 0.015-0.98), p 0.03)] (Figure 1A). On the other hand, we detected 2 clinically-relevant non-major bleeding in patients treated with reduced dose DOACS [4.7% (95%CI, 5.5-17.2)] and 2 in patients who continued full-dose anticoagulation [2.8% (95%CI 0.34-10.2)] with HR 0.25 (95% CI, 0.024-2.59) (Figure 1B). No

bleeding episodes were detected in patients who stopped anticoagulation.

Conclusions: Recurrence rate of VTE in patients with severe hereditary thrombophilia under treatment with reduced doses of DOACs was reduced but without statistically significance difference compared to the rate of patients who stopped anticoagulation. On the other hand, the rate of bleeding complications was similar between patients who continued full-dose and patients undergoing reduced doses. Further data are needed before we can suggest the use of reduced-dose DOACs in patients with severe hereditary thrombophilia.

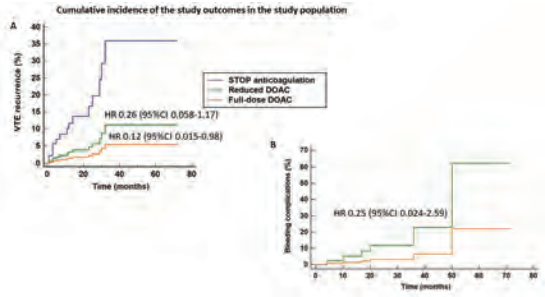

Figure 1.

CO098

REVERSAL THERAPY IN EARLY MANAGEMENT OF SEVERE HEMORRHAGE IN PATIENTS UNDER DIRECT ORAL ANTICOAGULATION THERAPY: MORE ON OF ANDEXANET ALFA *VS.* 4F-PCC

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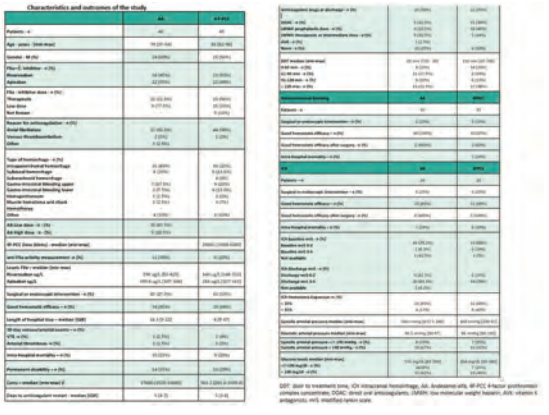
Background and Aims: Andexanet alfa (AA) became available in Italy in 2021 for the reversal of major bleeding associated with rivaroxaban and apixaban. However, 4-factor prothrombin complex concentrate (4F-PCC) is routinely used in many Centres for this indication because of higher availability and lower cost. Data on AA from everyday clinical practice are lacking. The aim of the study is to evaluate efficacy, safety and clinical outcomes of AA and 4F-PCC for the early management of apixaban or rivaroxaban-associated acute major bleeding in every-day clinical practice.

Methods: This single-center prospective cohort study included all adult patients with severe traumatic or spontaneous rivaroxaban or apixaban-related hemorrhage who received AA or 4F-PCC as a reversal strategy. Our primary analysis evaluated the achievement of hemostatic efficacy. Particularly, good hemostasis for cerebral hemorrhage (ICH) was defined as ≤35% increase in hematoma volume, whereas for other major bleeding events as stable hemoglobin level and no need for further transfusion or invasive interventions at 48 h. Secondary outcomes included 30-day mortality, permanent disability (Modified Rankin Scale >/= 3), length of hospital stay, incidence of thromboembolic events and costs. Outcomes were separately analyzed for gastrointestinal (GI) and ICH bleeding.

Results: 85 patients (median age 80 years, M=61%) were included, of whom 40 (47%) received AA and 45 (53%) received 4F-PCC. Patients treated with 4F-PCC were older than those treated with AA (p=0.02), while other clinical characteristics, including site of major bleeding, were comparable between groups (Table 1). Overall, the achieved hemostatic efficacy was good in 34 (85%) patients in AA group *vs* 29 (64%) patients in 4F-PCC group (p=0.03). 10 patients (25%) treated with AA died during hospitalization *vs* 9 (20%) treated with 4F-PCC (p= 0.59) and there was no significant difference in the rate of permanent disability [AA 14 (35%) *vs* 4-FPCC 13 (29%) (p=0.55)]. Length of stay was slightly longer AA *vs* 4F-PCC group (p= 0.13). 5 patients (5% AA *vs* 7% 4F-PCC, p=0.77) had thrombotic complications, namely 3 venous thromboembolism events (2.5% AA *vs* 4% 4F-PCC) and 2 arterial events (2.5% AA *vs* 2% 4-FPCC) occurred. Costs were higher with AA *vs.* 4F-PCC. All the patients with GI bleeding treated with AA achieved hemostatic efficacy (AA 100% *vs* 4F-PCC 67%, p=0.056). Considering only patients with ICH (24 treated with AA *vs* 20 with 4F-PCC), door to treatment times (DDT) was comparable, 29 patients (66%) had systolic blood pressure levels >140 mmhg (median 160 mmhg) but only 17 (46% AA *vs* 46% 4F-PCC) were treated with antihypertensive drugs; no difference in hemostatic efficacy (83% AA *vs* 60% 4F-PCC, p=0.18), and intra-hospital mortality (29% *vs* 30%, respectively, p=0.95) were detected. Interestingly, all patients (28%) undergoing neurosurgery obtained good hemostasis (AA 100% *vs* 4F-PCC 100%). 65% of patients resumed anticoagulation after a median of 5 days. 35 patients were discharged with low-molecular weight heparin, 16 with a direct oral anticoagulant, and 1 with warfarin.

Table 1.



Conclusions: Real-world data showed that AA was more effective than 4F-PCC to achieve hemostasis. Safety is

comparable. All patients with GI bleeding treated with AA had an optimal hemostasis. Disability and mortality in patients with ICH were high despite reversal agents used but DDT, glucose and blood pressure control are suboptimal.

CO099

RIVAROXABAN IN PAEDIATRIC VENOUS MALFORMATIONS: PRELIMINARY DATA FROM A RETROSPECTIVE SINGLE-CENTER STUDY

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Background and Aims: Venous malformations (VMs) are the most frequent type among congenital vascular malformations, with an incidence between 0.8-1%. VMs can be cutaneous and extracutaneous, single or multiple; typically, VMs appear from birth, show progressive growth and persist throughout life. Therefore, they require a multidisciplinary approach to ensure early diagnosis and prevent or treat any complications. We report preliminary data from our center's experience with the use of rivaroxaban in pediatric venous malformations complicated by thrombosis.
Methods: We conducted a retrospective observational single-center study at Bambino Gesù Children's Hospital. Data were collected from patients <18 years old with venous malformations complicated by thrombosis treated with rivaroxaban, during the period from September 2022 to February 2024. Primary outcome was to evaluate improvement, resolution or progression of venous thrombosis, in patients treated with rivaroxaban. Secondary outcome was to assess symptomatic recurrences in patients undergoing secondary prophylaxis. Clinical follow-up was performed at 3,6,12 months and imaging reevaluation at 6 and 12 months.
Results: Rivaroxaban was used for the treatment of acute venous thrombosis in 30 patients, after at least 5 days of parenteral anticoagulant therapy, and for secondary prophylaxis in 5 patients. Thrombophilia was found in 23 (66%) patients by hemocoagulative screening. The safety and efficacy of rivaroxaban were evaluated in all 35 enrolled patients; no patient was lost to follow-up. Twenty-seven (90%) patients treated with rivaroxaban, reassessed at 3 to 6 months, reported complete regression of pain due to thrombosis. Among them, 71% had been previously treated with acetylsalicylic acid, with no improvement in pain symptoms and subsequent development of thrombosis. Two patients reported occasional pain and one persistence of pain symptoms after 3 months. Among the five patients on secondary prophylaxis, one had symptomatic recurrence 12 months after starting rivaroxaban, with recent onset of thrombosis detected on ultrasound. Sixteen (46%) patients showed complete resolution of thrombosis at the end of treatment period; imaging improvement with almost complete recanalisation was observed in 11 (31%) patients. Two (5.7%) patients showed unchanged imaging with persistence of thrombosis at 6 months, while one patient developed thrombosis after 12 months of secondary prophylaxis. Five patients have not yet had ultrasound re-evaluation. Thirty-one (89%) patients experienced no side effects. Three patients reported nausea and diarrhea a few days after starting treatment, which resolved by halving the dose for 2 weeks; no further gastrointestinal symptoms after resuming the initial dose. One girl complained of menorrhagia in the first 3 menstrual cycles after starting rivaroxaban.
Conclusions: Preliminary data of our study showed that rivaroxaban was safe and effective in paediatric patients with complicated venous malformations or at risk of thrombotic recurrence. To date, bodyweight-adjusted rivaroxaban regimens are a viable alternative to standard anticoagulants, especially in patients requiring prolonged treatment, because they are available in oral formulations (oral suspension granules and tablets) and do not require laboratory monitoring.

CO100

DIRECT ORAL ANTICOAGULANTS IN COMPARISON WITH VITAMIN K ANTAGONISTS AND ANTIPLATELET AGENTS ON TIMING AND OUTCOMES IN HIP FRACTURE SURGERY PATIENTS OLDER THAN 65: THE ORTHO-GER-DOAC STUDY

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Background: Surgery within 48 hours after admission

of patients older than 65 years for hip fracture is inversely related to mortality. In subjects on direct oral anticoagulants (DOAC), current guidelines suggest waiting at least 48 hours after stopping Factor Xa inhibitors and up to 96 hours for dabigatran before surgery at high risk of bleeding, without drug testing.

Aims: To assess whether drug measurement in the elderly with hip fracture and on DOAC allows surgery within 48 hours when compared with subjects taking vitamin K antagonists (VKA) or antiplatelet agents or no antithrombotic drug.

Methods: A retrospective observational cohort study was conducted in hip fracture subjects above 65 years admitted to three Orthogeriatric Units in Italy from 2015 to 2022. At admission, demographic and comorbid conditions were collected and all antithrombotic agents were stopped. Patients on VKA had INR tested and received vitamin K to obtain an International Normalized ratio (INR <1.5). Patients on DOAC enrolled until 2018 underwent daily drug testing and surgery was performed only after DOAC levels were near or below trough levels. Days from hospital admission to surgery and peri-operative total blood loss were calculated. Major bleeding complications during hospital stay and all-cause mortality within 90 days were recorded.

Results: Among 747 patients (median age 85; Interquartile Range:81-89), a significantly lower proportion of patients on DOAC (65.5%) underwent surgery within 48 h after admission, when compared with patients on antiplatelet agents (88.6%) or VKA (73.3%). Pre-operative DOAC measurement significantly delayed timing to surgery (3.18 days *vs* 2.42: P <0.05). Major bleeding and mortality rates at 90 days were similar in the subgroups of patients according to the type of antithrombotic drug. Peri-operative mean and median blood loss was highest in subjects who were taking DOAC, regardless of drug measurement, when compared with patients either on antiplatelet agents or on VKA.

Conclusions: DOAC measurement delays hip fracture surgery while DOAC are associated with a significantly higher total blood loss, even in subjects with low presurgical DOAC levels.

CO101

EFFECTIVENESS AND SAFETY OF REDUCED DOSE OF DIRECT ANTICOAGULANT FOR VENOUS THROMBOEMBOLISM DURING A LONGER THAN 3 YEARS FOLLOW-UP

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Background and Aims: Reduced dose of direct oral anticoagulants (DOACs) for venous thromboembolism (VTE) is often used after completed standard-intensity treatment, however there are limited data beyond the first year of their use. Our study aims to evaluate the effectiveness and safety of reduced dose of DOACs for long-term secondary prevention of VTE.

Methods: We performed a preliminary retrospective analysis of patients prospectively followed in our outpatients clinic. Patients were included if they received reduced dose of DOACs and had at least one year of follow-up. Duration of follow-up was calculated until the development of an outcome of interest or until last available clinical contact, whichever came first. Effectiveness outcomes were recurrent VTE and arterial events (*i.e.*, acute myocardial infarction, acute ischemic stroke or transient ischemic attack). Safety outcomes were major, clinically-relevant non-major, and minor blessings. Baseline characteristics of the enrolled population and outcomes of interest were reported as descriptive statistics and divided into patients with a history of provoked and unprovoked VTE.

Results: Our analysis included 108 patients, of whom 74 had provoked and 34 unprovoked thrombosis. Population characteristics are shown in Table 1. The mean age and mean BMI were found to be higher in the unprovoked group, while the sex distribution was found to be comparable between the two groups. More patients with personal and family history of VTE were found to be present in the provoked thrombosis group. Roughly 20% and 10% of patients with provoked thrombosis had previous and active cancer, respectively. The most represented VTE in both populations was in the lower limbs, followed by isolated pulmonary embolism and lower limb thrombosis with pulmonary embolism. A smaller proportion of patients in both groups were being treated for upper extremity venous thrombosis, with or without embolism. The most widely used anticoagulant in both groups was apixaban followed by rivaroxaban. Mean follow-up duration was 1244 days. Regarding efficacy outcomes, the incidence of arterial events was higher than the incidence of VTE recurrence with a slightly higher incidence of both venous and arterial events in patients with provoked than unprovoked thrombosis. One recurrent VTE and three arterial events occurred beyond the first year of therapy. Instead, the incidences of major, clinically relevant nonmajor and minor bleeding were slightly higher in patients with unprovoked thrombosis. All but one clinically-relevant non-major bleeding occurred beyond the first one year of therapy.

Conclusions: In this preliminary analysis, reduced dose of DOACs appeared to have an acceptable effectiveness and safety profile behind the first year of follow-up. Incidences of thrombotic events was slightly higher and that of bleedings slightly lower in patients with provoked than unprovoked thrombosis.

Table 1.

Baseline patients' characteristics

Variables	Overall N = 108	Provoked N = 74	Unprovoked N = 34	p-values
Median age, years [IQR]	76 [63, 82]	74 [60, 81]	82 [72, 88]	0.001
Female sex, n (%)	57 (52.8)	39 (52.7)	18 (52.9)	1.000
Median BMI, [IQR]	26 [24, 30]	26 [24, 29]	28 [24, 31]	0.452
Smoking habit, n (%)				0.454
Never	60 (69.8)	43 (72.9)	17 (63.0)	
Current	25 (29.1)	15 (25.4)	10 (37.0)	
Former	1 (1.2)	1 (1.7)	0	
Previous cancer, n (%)	15 (14.2)	13 (17.8)	0	0.192
Active cancer, n (%)	5 (9.4)	4 (10.8)	0	0.992
Personal history of TEV, n (%)	42 (39.6)	30 (41.1)	12 (36.4)	0.805
Family history of TEV, n (%)	9 (10.1)	7 (10.9)	2 (8.0)	0.982
History of bleeding, n (%)	2 (1.9)	1 (1.4)	1 (3.1)	1.000
Site of TEV, n (%)				0.369
PE	31 (28.7)	20 (27.0)	11 (32.4)	
LEDVT	43 (39.8)	32 (43.2)	11 (32.4)	
LEDVT + PE	21 (19.4)	11 (14.9)	10 (29.4)	
UEDVT	4 (3.7)	4 (5.4)	0	
UEDVT + PE	2 (1.9)	5 (7.0)	2 (5.9)	
Other sites	7 (6.5)	6 (5.7)	0	
Type of DOAC				0.424
Apixaban	87 (80.6)	57 (77.0)	30 (88.2)	
Dabigatran	5 (4.6)	5 (6.8)	0	
Edoxaban	1 (0.9)	0	1 (2.9)	
Rivaroxaban	15 (13.9)	12 (16.2)	3 (8.8)	
Outcomes				
Recurrent VTE	2 (1.9)	2 (2.7)	0	0.842
Arterial events	5 (4.6)	4 (5.4)	1 (2.9)	0.942
Major bleedings	4 (3.8)	2 (2.7)	2 (6.5)	0.101
CRNMB	2 (1.9)	0	2 (6.5)	0.101
Minor bleedings	2 (1.9)	1 (1.4)	1 (3.2)	0.101
Median follow-up, days [IQR]	1244 (694)	1249 (689)	1231 (714)	0.898

CO102

PREDICTORS OF 90-DAY MORTALITY IN PATIENTS WITH GASTROINTESTINAL BLEEDING ON DIRECT ORAL ANTICOAGULANT THERAPY

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Background and Aims: Gastrointestinal bleedings (GIB) are a clinically relevant complications in patients receiving long-term therapy with direct oral anticoagulant (DOAC), leading to substantial morbidity and mortality. Identifying predictors of mortality in patients experiencing a DOAC-associated GIB is crucial for developing targeted interventions and improving clinical outcomes. This study aimed to determine the predictors of 90-day mortality in patients who experience DOAC-associated GIB.

Methods: Information about clinical characteristics and endoscopic findings were prospectively captured by an electronic database at the time of the index event in patients admitted to hospital for DOACs-related GIBs. Univariate and multivariate logistic regression analyses were performed to identify significant predictors of 90-day mortality.

Results: 284 patients consecutively admitted to Hospital in Perugia for spontaneous DOACs-related GIBs were included in a prospective cohort study. At entry, the mean age was 81.7 years, with 41.5% female. The indication for DOAC treatment was atrial fibrillation in 86.5% of patients. Death at 90 days occurred in 51 patients (17.9%). The Charlson Comorbidity Index (CCI) was significantly higher in patients who died (mean 6.2) compared to survivors (mean 5.6; p=0.028). Platelet count (p=0.025) and shock index (SI)>1 (p=0.05) were significantly higher in patients who died at 90 days. In univariate analysis, significant predictors of 90-day mortality were CCI (OR=1.21, 95% CI 1.01-1.46, p=0.0345), platelet count (OR=1.00, 95% CI 1.00-1.00, p=0.0187), ischemic stroke within the last 6 months (OR=14.37, 95% CI 1.80-294.02, p=0.0222), dementia (OR=3.09, 95% CI 1.23-7.41, p=0.0131), and active cancer (OR=2.05, 95% CI 0.96-4.19, p=0.0534). Multivariate analysis confirmed platelet count (OR=1.00, 95% CI 1.00-1.00, p=0.0336), SI >1 (OR=4.02, 95% CI 1.11-13.78, p=0.0268), and active cancer (OR=14.04, 95% CI 2.31-124.83, p=0.0070) as independent predictors of 90-day mortality.

Conclusions: In our study, platelet count, SI>1, and active cancer emerged as significant independent predictors of 90-day mortality in patients experiencing DOAC-associated GIB.

CO103

PLEIOTROPIC EFFECTS OF ANTICOAGULANT THERAPY: IS THERE A DIFFERENCE BETWEEN AVK AND DOACS?

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Background: Atrial fibrillation (AF) is the most common supraventricular arrythmia in clinical practice. Emerging evidence suggests a significant role of inflammation in the pathogenesis and in the maintenance of AF, We hypothesize a different role of anticoagulant therapy (AVK. *vs.* DOACs) in reducing the levels of inflammatory biomarkers in AF.

Methods: The Strat-AF study is an observational, prospective, single-center hospital-based study enrolling patients with atrial fibrillation, aged 65 years

or older, and with no contraindications to undergo magnetic resonance imaging, referring to Center of Atherothrombotic Disease of our University Hospital (AOU Careggi) for the management of oral anticoagulation therapy. Recruited patients are evaluated by means of a comprehensive protocol, with clinical, cerebral magnetic resonance imaging and circulating biomarkers assessment. One of the main outcomes is the evaluation of the role of circulating biomarkers of inflammation (IL-6, IL-8, TNFα, IL-4, IL-10, CCL2, CXCL10, ICAM-1, VCAM-1, VEGF), haemostasis (PAI-1, CLT, vWF) and extracellular matrix remodeling (MMP-2, -7, -8, -9, -12, TIMP-1, -2, -3, -4) in relationship to the type of oral anticoagulant therapy. The results refer to 170 subjects [mean age 77.7±6.8 years, females n=59 (34.7%)] enrolled in the Strat-AF Study. The subjects of the study were all on oral anticoagulant therapy: 30.6% (n=52) were on VKA, whereas 69.4% (n=118) were on DOACs. Regarding those who were on AVK, 81.3% (n=39) of them had an adequate TTR (>60%), whereas, with regard to the patients anticoagulated with DOACs, we performed the dosage of each type of DOAC (apixaban, dabigatran, edoxaban, rivaroxaban) and discovered that in the majority of cases (>90%), the DOAC concentrations were in line with the average concentration reported in clinical studies.

Results: Patients treated with AVK had significantly lower circulating levels of IL-6 and of TNF-alpha (pro-inflammatory cytokines) and significantly lower circulating levels of IL-10 (anti-inflammatory cytokine) if compared to patients treated with DOACs [0.38 (0.30-1.21) pg/mL *vs.* 1.98 (1.42-3.58) pg/mL, p<0.001, 1.53 (0.59-2.28) pg/mL *vs.* 2.95 (1.51-5.00) pg/ml, p<0.001 and 1.45 (0.24-3.46) pg/mL *vs.* 3.29 (1.09-3.56) pg/mL, p=0.003, respectively]. The levels of ICAM-1 and VCAM-1 were significantly lower in AVK treated patients if compared to patients treated with DOACs [297.46 (247.84-385.63) pg/mL *vs.* 343.62 (273.42-601.88) pg/mL, p=0.023 and 1205.00 (971.11-1830.00) pg/mL *vs.* 1532.00 (1032.08-2148.13) pg/mL, p=0.036, respectively]. Moreover, in patients treated with AVK, PAI-1 levels and values of ETP (endogenous thrombin potential) ratio (TM+/-) were significantly higher than in patients receiving DOACs [11.33 (7.83-18.32) *vs.* 8.64 (6.83-12.53), p=0.020 and 0.87 (0.68-1.01) *vs.* 0.65 (0.41-0.90), p<0.001, respectively]. Lastly, the circulating levels of MMP-12 were significantly lower in AVK treated patients if compared to patients treated with DOACs [79.35 (45.01-93.91) *vs.* 450.10 (309.12-612.28), p<0.001].

Conclusions: These results from Strat-AF study may be an essential step towards the exploration of the role and the contribute of anticoagulant therapy in reducing inflammation-related biomarkers in AF patients. In particular, these results suggest a pleiotropic role of AVK: identifying a possible effect of these drugs on coagulation and inflammation pathways could pave the way for clinical-therapeutic scenarios.

CO104

HYPERCOAGULABLE STATE STUDIED BY THE PERFORMANCE OF CLOT WAVEFORM ANALYSIS, THROMBIN GENERATION AND CLOT TEXTURE BY SCANNING ELECTRON MICROSCOPE

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Background and Aims: Activated partial thromboplastin time (aPTT) is a coagulative screening test used to investigate mainly hypocoagulable conditions. Clot Waveform Analysis (CWA) of aPTT can generate clotting curves showing the dynamic process leading to fibrin formation, thus providing information on essential parameters other than clotting times and revealing the "hidden" features of aPTT. This study aimed to detect both CWA and Thrombin Generation (TG) along with clot texture by Scanning Electron Microscope (SEM) in different groups of patients with a hypercoagulable state and a group of Healthy Controls (HC). The main aim of this study was to investigate whether CWA could be a new laboratory tool for flanking the TG and Clot Scanning by SEM in the assessment of hypercoagulability.

Methods: Activated Partial Thromboplastin (aPTT) ratio, CWA, the thrombin generation assays (TG), and the clots' scanning by SEM were detected in 126 patients (51 Systemic Sclerosis, 51 Liver Cirrhosis, 13 High Padua Prediction Score (PPS) without anti-thrombotic prophylaxis) and 42 healthy control. Texture analysis for images acquired by SEM was performed using MATLAB software. Data are described as median and range. ANOVA (Kruskal-Wallis) followed by Dunn's test was used to show possible differences among the groups.

Results: Compared to HC, patients with SSc and High PPS showed higher levels of CWA, Thrombin generation, and thicker clots by SEM. (Table 1).

Conclusions: We have shown how clot texture, TG, and CWA are consonant in detecting a hypercoagulable state. CWA can detect this condition as TG and clot texture do. This is important because CWA is a rapid and easy test, even in non-specialized laboratories. Moreover, it is inexpensive in comparison with the other two methods employed here. TG needs an expensive machine and a long procedure. Even worse is the impact of the clot texture by SEM which, although fascinating, requires a long and often difficult methodology for providing reliable results. The primary finding presented in this abstract are based on the dissertation of Dr. Maria Filomena Ruberto

for the II Level Master's Degree in Hemostasis and Thrombosis, which she received from the Catholic University in Rome, Italy, in conjunction with the Società Italiana per lo Studio dell'Emostasi e Trombosi (SISET), in November 2023.

Table 1.

Parameters (median and range)	Systemic Sclerosis n=51	Liver Cirrhosis n=51	High PPS n=13	Healthy Controls n=42
aPTT ratio	0.96, 0.83-1.15	1.07, 0.89-1.40	0.93, 0.71-1.66	1.00, 0.84-1.25
1st der aPTT (mAbs/s)	260.4, 161.2-380.7*	204.5, 69.2-468.3	368.2, 104.2-612.5*	224.2, 137.3-359.5
2nd der aPTT (mAbs/s²)	969.7, 565.1-1465.8*	693.1, 220.8-1970.1	1524.1, 264.6-2289.8*	788.15, 458.1-1233.8
ETP ratio	0.70, 0.29-1.36*	0.73, 0.30-1.34*	0.84, 0.68-1.05*	0.56, 0.32-0.90
Contrast (A.U.)	0.22, 0.18-0.29*	0.39, 0.17-0.83	0.17, 0.15-0.25*	0.36, 0.20-0.54

ANOVA (Kruskal-Wallis) and Dunn's test (*post-hoc analysis*), p<0.000001
*P<0.05 vs HC

CO105

RITUXIMAB IN LUPUS ANTICOAGULANT HYPOPROTHROMBINEMIA SYNDROME. A CASE REPORT

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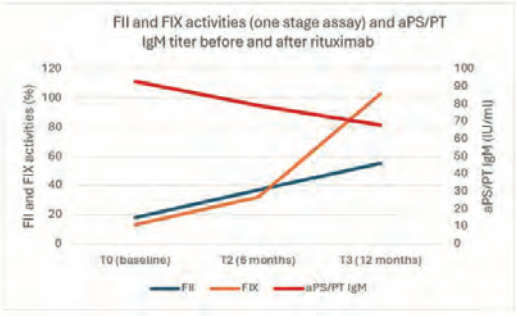
Background: Lupus anticoagulant hypoprothrombinemia syndrome (LAHPS) is a rare autoimmune condition associated with antiphospholipid syndrome (APS). LAHPS is characterized by bleeding tendency due to autoantibodies against prothrombin (FII), which belong to antiphospholipid antibodies (aPL). Correlation between thrombotic APS (TAPS) and positive anti-phosphatidylserine/prothrombin antibodies (aPT/PS) was confirmed by the International Society of Thrombosis and Hemostasis APS subcommittee. In a few cases, aPS/PT bind to a nonactive portion of the molecule, resulting in accelerated clearance of prothrombin and significant clinical bleeding. Immunosuppressive therapies are considered essential in LAHPS.

Case Report: This report describes a 34-year-old woman with positive Lupus anticoagulant (LA) test and high titer anticardiolipin antibodies Immunoglobulin G (ACA IgG) and anti-β2 glycoprotein I antibodies IgG (aB2GPI IgG). Severe anemia secondary to heavy menstrual bleeding (HMB) was diagnosed, necessitating intravenous iron administrations and blood transfusions. Prothrombin time ratio (PT) and activated partial thromboplastin time ratio (aPTT) were 1.4 and 1.85 (normal value 0.8-1.2 and 0.82-1.18 respectively). Gynecological causes of HMB and other bleeding disorders were excluded. LA test was positive (DVVT ratio 3.54, DVVT mix ratio 3.79, DVVT confirm ratio 2.59, SCT ratio 4.48, SCR mix ratio 5.34, SCT confirm ratio 2.43, normal values <1.2), with high titer ACA and aB2GPI IgG (2371 and 15113U/ml respectively, normal values<20U/ml) and low titer ACA and aB2GPI IgM. Moderate-severe FII deficiency was Found (18%) and LAHPS was suspected; FIX deficiency was also found (6%), without FIX inhibitors. aPS/PT assay was performed in Padua research lab (IgG 230 U/ml and IgM 93 U/ml). Based on these findings, immunosuppressive and hormonal therapies were proposed. She refused steroids, intravenous Ig infusion and intrauterine device (IUD), so rituximab 375mg/m²/week x4 weeks and desogestrel 75mcg/day were started. FII and FIX activity and aPL titers were monitored at the end of rituximab cycle (T1), 2 (T2) and 12 (T3) months later. A gradual increase in FII and FIX level at T2 and T3 and a reducing trend in aPL IgG titers at T1 and T3 were observed. aPS/PT titer was reassessed 6 months and 12 months after rituximab (IgG/IgM 201/79 and IgG/IgM 235/68 U/ml respectively) demonstrating a moderate decrease in IgM (Figure 1). One year after, hormonal therapy was stopped: no significant bleedings were observed.

Conclusions: LAHPS is a rare autoimmune condition without defined therapeutic guidelines. In this case, complete clinical response and partial serological response were observed after rituximab treatment. This study examined aPS/PT IgG and IgM titers before and after immunosuppressive therapy, revealing a modest decrease in IgM isotype. This finding supports the hypothesis of antibody-mediated accelerated clearance of prothrombin, rather than direct antibody-mediated inhibition of FII activity. A possible explanation is that only a part of aPS/PT antibodies were decreased allowing the rise of factor II. aPS/PT comprise different types of anti-prothrombin antibodies. These specific portion of aPS/PT antibodies could be directed against the GLA-domain part of prothrombin, a fact that could justify the marked decrease of the vitamin-K dependent factors. Rituximab probably reduces these specific antibodies, led to factor activity normalization.



FII and FIX activities (one stage assay) and aPS/PT IgM titer before and after rituximab

Figure 1.

CO106

RISK FACTORS FOR DAMAGE ACCRUAL IN PRIMARY ANTIPHOSPHOLIPID SYNDROME: A RETROSPECTIVE SINGLE-CENTER COHORT STUDY

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Background and Aims: Despite anticoagulant therapy, antiphospholipid syndrome (APS) has a higher rate of recurrent events, leading to potentially accrued damage and a negative impact on life quality. In the attempt to identify risk factors associated with damage accrual we evaluate laboratory and clinical features of APS as well as traditional cardiovascular risk factor and damage accrual.

Patients and Methods: We conducted a retrospective cohort study enrolling PAPS patients attending the Thrombotic and Hemorrhagic and/or Rheumatology Units, Department of Medicine at the University of Padua from 1991 until June 2023. All patients were retrospectively classified according to the Sidney updated criteria. Medical records of 282 APS patients, with a median age of 36 (IQR 30-46) years, followed by a median of 195 (IQR 137 – 272) months were reviewed. The primary endpoint was damage accrual during follow-up, defined as organ/tissue impairment present for at least six months or caused permanent loss. The secondary endpoints were damage burden at baseline, defined as organ damage within six months of disease onset, lasting at least six months from the index event, or causing permanent loss.

Results: Eighty (28.4%) patients presented damage accrual. Almost half, 42 (52.5%) of the patients, presented organ damage within the first six months after APS onset, and 41.3% had more than one organ involved. Neuropsychiatric involvement, with 38.8% of the patients, was the most frequent, followed by peripheral vasculopathy and renal involvement, 35% each. Death happened in 7 (2.5%) patients; damage accrual was associated with a 6-fold risk of death [OR 6.7 (95% CI 1.3-35.1), p=0.03]. Instead, there was no association between death and damage burden at baseline. The Kaplan-Meier curves showing the estimated survival probability of PAPS patients with damage burden at baseline and those with damage accrual at follow-up are reported in Figure 1 A and B. Microangiopathy and non-criteria manifestations were independent risk factors for damage accrual with 5-fold and 4-fold higher risk, respectively [(OR 4.9 (95% CI 2.1-11.7), p<0.0001 and (OR 3.8 (95% CI 1.5-10.1), p=0.007]. The cumulative incidence of damage accrual increased by 5.7-fold and 3.6-fold in patients with microangiopathy and non-criteria manifestations. Fifty-seven (20.2%) patients had developed organ damage after six months of disease onset; one-third of them, 19 (33.3%), developed a further organ impairment during follow-up. Microangiopathy and non-criteria manifestations determined around 6-fold increased risk of a new organ impairment in PAPS patients, respectively [OR 5.8 (95% CI 1.4-21.9), p=0.02 and OR 6.5 (95% CI 1.6-22.1), p=0.009].

Conclusions: PAPS patients showed a higher damage accrual rate; half presented within six months from disease onset. Microangiopathy and non-criteria manifestations were independent risk factors for damage accrual regardless of APS clinical subsets, laboratory profile, and first thrombotic event. These findings should be considered when counseling APS patients and help guide clinicians' therapeutic decisions.

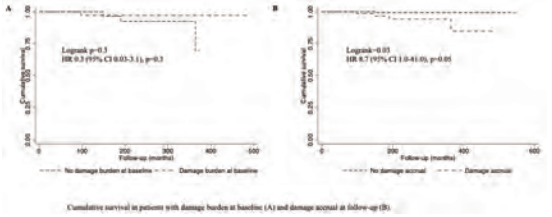

Figure 1.

CO107

ANTIPHOSPHOLIPID NEPHROPATHY IS ASSOCIATED WITH AN INCREASED RISK OF RENAL INSUFFICIENCY. A SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS

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Background and Aims: The entire renal vasculature could be affected by antiphospholipid syndrome (APS), ranging from thrombosis of renal arteries and veins to microvascular injuries involving glomeruli and terminal portions of the arterial vasculature and arterioles. Antiphospholipid antibodies (aPL) nephropathy (aPL-N) is a complex feature of antiphospholipid syndrome due to microvascular lesions. Renal prognosis and predictors of outcome are not yet known.

Patients and Methods: We performed a systematic review of the literature (February 2006-January 2024) using Pubmed, Scopus, Cochrane Library, and EMBASE databases. Two reviewers independently conducted literature screening and data extraction in a blinded, standardized manner. A random-effects model was used to pool odds ratio (OR) (with 95% CI) for the primary analysis, the risk of renal insufficiency. Subgroup analyses were performed for clinical and laboratory features that predicted renal outcomes. Heterogeneity was assessed by I2%.

Results: Eight-hundred and ninety-nine patients yielded from 9 records were included in the systematic literature review; 297 (33.0%) fulfilled the Updated Sapporo classification criteria for APS. Biopsy-proven aPL-N was found in 238/832 (28.6%). Acute kidney insufficiency (AKI) was present at diagnosis in 20/65 (30.8%), while 73/233 (31.3%) patients with aPL-N developed chronic

kidney disease/end-stage kidney disease (CKD/ESKD) at follow-up. Arterial hypertension and mild proteinuria (<2,5 g/24 h) were the most presented clinical manifestations at diagnosis, respectively, at 73% and 66.7%. Acute lesions defined as thrombotic microangiopathy were present in 102/210 (48.6%) of the patients. The most frequent chronic lesion was FIH presented in 138/208 (66.3%). Interestingly, 69/111(62.2%) biopsies showed the co-existence of membranous glomerulonephritis. Six records involving 709 patients were included in the meta-analysis. Pooled analysis showed that APL-N was associated with an increased risk of CKD/ESKD [OR 6.89, 95% CI: 2.42-19.58] and AKI [OR 2.97, 95% CI: 1-4-6.29]. Furthermore, arterial hypertension and positivity for LAC, aCL, and anti-beta2GPI antibodies were associated with an increased risk of developing aPL-N [OR 3.7, 95% CI: 1.9-7.23], [OR 4.01, 95% CI: 1.88-8.53], [OR 2.35, 95% CI: 1.31-4.21] and [OR 19.2, 95% CI: 2.91-125.75], respectively. Pooled analysis regarding triple aPL positivity was not possible because only one study reported the association between aPL-N and triple aPL positivity.

Conclusions: This meta-analysis summarizes the current evidence on the impact of aPL-N on renal outcome and available predictors of renal outcome. Pooled analysis showed that aPL-N is associated with poor renal outcomes. High blood pressure and aPL positivity have been identified as predictors of adverse renal outcomes. It is urgently necessary to perform methodologically rigorous multicenter studies on aPL-N in PAPS patients. Meanwhile, the presented results provide clinicians with updated knowledge on renal outcomes and predictors of renal outcomes in aPL-N, enabling a personalized follow-up and therapeutic approach.

CO108

CENTRAL ROLE OF LOW-GRADE INFLAMMATION IN MEDIATING THE 2GPI-DEPENDENT IGG EFFECT ON THE PLATELET ACTIVATION PHENOTYPE CHARACTERISTIC OF PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background and Aim: Antiphospholipid antibodies (aPL), causing endothelial perturbation, lead to platelet activation and thrombo-inflammation responsible for the thrombotic vasculopathy of antiphospholipid syndrome (APS). The mechanisms behind aPL-mediated platelet activation are not completely known. This study aimed to gain insights into primary APS (PAPS) pathogenesis by further characterizing the role of low-grade inflammation in sustaining the platelet prothrombotic profile and evaluating how hydroxychloroquine, anti-inflammatory and antiplatelets drugs can modulate it.

Methods: We enrolled 37 PAPS at first diagnosis, with medium to high aPL levels. 24 patients experienced vascular symptoms, 8 patients had both vascular and obstetric symptoms. 13/24 PAPS were on vitamin K antagonists while 8/24 were on anti-platelet therapy only. 34 healthy subjects (HS) were included as controls. Platelet P-Selectin, aGPIIbIIIa, platelet-leukocyte aggregate (PLA), ApoER2, β2GPI expression and membrane and intracellular Tissue Factor (TF) and TFPI, as indicators of a procoagulant platelet phenotype, were analyzed by whole blood flow cytometry. IL-6 levels were assessed in plasma by ELISA. The impact of PAPS plasma and β2GPI-dependent IgG on platelet activation and PLA formation was evaluated in *ex vivo* mixing experiments where the pharmacological modulation of the platelet activated phenotype was also assessed.

Results: PAPS patients had a 2-fold greater P-selectin+ ($p<0.05$) and aGPIIbIIIa+ ($p<0.01$) platelets as well as platelet-granulocyte (PGA, $p<0.001$) and platelet-monocyte (PMA, $p<0.05$) aggregates. A significantly greater number of TF+-platelets and -PLA was present in PAPS compared to HS ($p<0.05$). Conversely, the percentage of platelets with intracellular TF or carrying TFPI was comparable as it was the overall platelet activated phenotype upon ADP stimulation. PAPS also had a 3-fold greater number of ApoER2+ and β2GPI+ platelets ($p<0.001$) compared to HS. Plasma IL-6 was on average within the reference range for HS, although 30% of PAPS had levels above the upper limit. In *ex vivo* mixing experiments, PAPS plasma added to HS platelets upregulated platelet activation markers, TF expression and PLA formation ($p<0.05$). Unexpectedly, β2GPI-dependent IgG upregulated only platelet TF exposure (3-fold; $p<0.001$), being the other platelet activation markers induced only upon IL-6 addition to the experimental system. Of note, IL-6 alone did not mimic the platelet phenotype observed in PAPS. Platelet incubation with ApoER2 inhibitor RAP, tocilizumab, as well as aspirin and P2Y12 inhibitor significantly inhibited P-selectin, aGPIIbIIIa, TF, PGA and PMA up-regulation induced by PAPS plasma and PAPS IgG. In contrast, it is worth mentioning that hydroxychloroquine blocked P-selectin, aGPIIbIIIa and PLA upregulation but did not affect TF expression and thus the prothrombotic platelet phenotype.

Conclusions: This study shows for the first time that a low-grade inflammation, mainly mediated by IL-6, is necessary for aPL to exert their pathophysiological role in inducing the platelet prothrombotic/proinflammatory phenotype characteristic of patients with APS. This synergistic mechanism is fully prevented *in vitro* by tocilizumab as well as by antiplatelet drugs but not by hydroxychloroquine. These findings provide the scientific rationale for new clinical studies designed to test a combined pharmacological approach rather than the use of monotherapy.

CO109

ISOLATED LUPUS ANTICOAGULANT (LA) POSITIVITY: ARE ANTI-PHOSPHATIDYL-SERINE/ PROTHROMBIN ANTIBODIES (APS/PT) CLINICALLY USEFUL?

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Background and Aims: Anti phosphatidylserine/prothrombin antibodies (aPS/PT) are often present in patients with antiphospholipid syndrome (APS) and might be relevant in the pathogenesis of this condition. They are major determinant of lupus anticoagulant (LA) in triple-positive antiphospholipid (aPL) profile. Whether they are present and pathogenic in patients with isolated LA, characterized by negative anticardiolipin (aCL) and anti β2-glycoprotein I (aβ2GPI) antibodies, is a matter of debate. The purpose of our study is to investigate the correlation of aPS/PT antibodies in those patients with isolated and/or borderline LAC.
Materials and Methods: The study was carried out on 31 patients who came to the outpatient clinic of atherothrombotic diseases of the University Hospital of Careggi, Florence, for: lengthened aPTT, rheumatological disease, high-risk pregnancy. LA was assessed by two test systems, the dilute Russell Viper Venom Time (dRVVT) and the Silica Clotting Time (SCT). Only patients with samples persistently positive over time (12 weeks) were considered LAC positive. All patients were negative for aCL and aβ2GPI antibodies. This cohort of 31 patients was analyzed for aPS/PT IgG and aPS/PT IgM with QUANTA Lite ELISA. The ELISA was performed manually with Infinity M200 System plate reader.
Results: Of the 31 patients, only 11 had positivity to both LAC and aPS/PT antibodies. The median age of the test population is 60 years (IQR 36-72 y). The sex prevalence is female (8/11, 72.7%). In both cases there is no significant difference. Correlation analysis performed on the cohort of 31 patients showed a borderline significant correlation between LAC sct and aPS/PT IgG antibodies (r2=0.1459, p=0.034). We observed that in strongly positive LAC (SCT and/or DRVVT >3 normalized ratio) there is strong positivity to both isoforms of aPS/PT antibodies (aPS/PT IgG and IgM >150.0 U/mL). In LAC-positive patients with borderline SCT and/or DRVVT values (mean 1.24 RT), the aPS/PT IgM antibody value was above the cut-off of positivity (mean aPS/PT IgM 48 U/mL).
Conclusions: To date, the small sample size does not allow us to draw unambiguous conclusions. However, the requirement for aPS/PT antibodies may be useful to confirm the clinical value of the thrombotic risk of borderline LAC and assessing whether a preventive therapeutic approach (*i.e.* antiplatelet therapy) is needed. For future studies, it will be important to further investigate this correlation to confirm our preliminary data.

CO110

SARS-COV-2 INFECTED LIVER PERICYTES STIMULATE VWF EXPRESSION BY PORTAL ENDOTHELIAL CELLS AND AN ANGIOGENIC RESPONSE IN THE PULMONARY ENDOTHELIUM

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Background and Aims: Severe SARS-CoV-2 infection can lead to the formation of systemic microthrombosis with alterations in the vascular component of several organs, including the liver. In the liver, the involvement of the portal vasculature may be associated with the development of intrapulmonary vascular dilatations and worsening of hypoxemia, featuring the hepatopulmonary syndrome. Previous observations indicate that, in COVID-19, alterations in the pulmonary circulation with persistent hypoxemia were observed. Starting from the emerging role of pericytes, mesenchymal cells intimately associated with the endothelium, in the pathophysiology of hepatic vascular lesions, in this study we tested the hypothesis that liver pericytes infected by SARS-CoV-2 induce a pro-coagulant phenotype eventually sustaining an angiogenic response of the pulmonary circulation.
Methods: Immunofluorescence (IF) of liver specimens from COVID-19 autopsies (n=16) and controls (n=17) was used to study the expression of SARS-CoV-2 spike (SP) or nuclear (NP) proteis with von Willebrand Factor (vWF) and PDGFR-β (pericyte marker). By mean fluorescence intensity, we quantified the expression levels of viral SP/NP in endothelial cells and pericytes. Cultured pericytes were infected in the BSL-3 facility with SARS-CoV-2 at the multiplicity of infection (MOI) of one or ten plaque forming units (PFU) per ml in starvation medium. Human umbilical vein endothelial cells (HUVEC) were grown to confluence, then medium was replaced with supernatants harvested from pericytes either uninfected or infected with SARS-CoV-2, and vWF expression quantified by confocal microscopy analysis. In addition, to assess the ability of vWF to stimulate the angiogenic component *in-vitro*, Human pulmonary microvascular endothelial cells (HPMEC) were cultured in plates pre-coated with Matrigel with standard medium, and treated

with recombinant human vWF protein. The total number of nodes and junctions, total tubule length and mean mesh size were analyzed using Angiogenesis Analyzer patch for ImageJ software.
Results: In the liver, PDGFR-β+ pericytes co-expressed viral SP and NP significantly more than endothelial cells lining the portal vasculature, which were more intensely decorated by vWF and contained extensive microthrombi compared with controls. Conditioned medium harvested from infected pericytes induced significant up-regulation of vWF in HUVEC (60.99±12.67 *vs* 27.57±11.06) and HPMEC (72.96±23.19 *vs* 18.85±10.75). Among angiogenesis parameters, treatment of 3D-tubular cultures of HPMECs with recombinant human vWF protein induced a significant enlargement of the mean tubule size as respect to untreated controls (1,5x), consistent with a vasodilation effect.
Conclusions: SARS-CoV-2 infection of liver pericytes leads to a local procoagulant response by up-regulating vWF in endothelial cells lining the portal vessels, likely contributing to portal microthrombosis. Moreover, vWF induced a significant increase in the tubule expansion of pulmonary endothelial cells, consistent with a vessel lumen widening effect relevant to intrapulmonary vascular dilations found in COVID-19 patients with severe hypoxemia. Thus, vWF released by portal endothelial cells may behave as a putative molecular effector linking hepatic lesions with pulmonary vascular perturbations in hepatopulmonary syndrome.

CO111

SARS-COV-2 INFECTED PERICYTES UP-REGULATE TF EXPRESSION LEADING TO SMALL PORTAL VESSEL MICROTHROMBI, WHICH ARE ASSOCIATED WITH INTRAPULMONARY VASCULAR DILATIONS

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Background and Aims: SARS-CoV-2 infection is associated with hypercoagulability that manifest as thromboembolic events affecting several organs inducing severe dysfunctions. Whereas the clinical impact of thromboembolic events in lung, heart and kidney is well-established, their effects on liver is less known. Histological analyses of hepatic samples obtained from patients who had died for respiratory failure in the first wave of COVID-19 pandemic, showed the presence of extensive thrombosis in the small branches of the portal vein, accompanied by a strong activation of pericytes, but negligible inflammation (endothelialitis). We aim to investigate whether pericytes can be infected by SARS-CoV-2 and if can be involved in the pathogenesis of portal microthrombosis found in the lethal forms of COVID-19.
Methods: Liver tissue obtained from COVID-19 autopsies (n=93) was tested via RT-PCR to assess the presence of SARS-CoV-2 RNA. By immunofluorescence (IF) we evaluated the expression of tissue factor (TF), an activator of the coagulation cascade, coupled with PDGFR-β (pericyte marker) and Spike protein (SP). Liver sections obtained from patients deceased for non-COVID-19 pneumonia-related respiratory failure served as controls. In lung specimens derived from the same autoptic series, we measured the presence of capillary luminal dilation and proliferation, as typical pulmonary lesions associated to hepatic diseases. Presence of microthrombi was assessed by Martius scarlet blue (MSB) stain for fibrin visualization in liver and lung tissue samples. Transmission electron microscopy (TEM) was used to confirm presence and distribution of SARS-CoV-2 virions in liver specimens. Cultured pericytes, infected with SARS-CoV-2 in a BSL-3 facility, will be used to evaluate ability of SARS-CoV-2 to infect cell cultures and to quantify TF expression by IF, real time PCR (rtPCR), and Western blotting (WB).
Results: In COVID-19-positive liver samples (n=16), high TF expression was selectively displayed by PDGFR-β+ cells rather than endothelial cells around the portal radicles harboring intraluminal thrombi, whereas no TF expression was observed in COVID-19-negative liver samples as well as in controls. By MSB stain, portal microthrombi were found in more than 75% of portal spaces, and were composed of fibrin/fibrinogen. Histological analysis of lung specimens showed diffuse capillary vasodilation and proliferation in lung specimens of patients with COVID-19-positive liver samples compared to COVID-19-negative liver samples (n=17), consistent with the presence of intrapulmonary shunts. Ultrastructural analysis of specimens from COVID-19-positive livers, showed intracellular vacuoles containing single viral particles in portal pericytes, in line with confocal microscopy analysis showing viral SP expression by PDGFR-β+ cells. *In-vitro* exposure of cultured pericytes to viral particles, confirmed their ability to be infected by SARS-CoV-2. Viral challenge induce a significant overexpression of TF by pericytes as respect to untreated controls (rtPCR: 0.013±0.002 *vs* 0.004±0.001, $p<0.01$; WB: 0.98±0.06 *vs* 0.55±0.18, $p<0.05$).
Conclusions: Liver pericytes abutting the small portal veins are infected by SARS-CoV-2, which induce them to overexpress TF. This local procoagulant response is associated with extensive portal microthrombosis and intrapulmonary vascular dilations, which may contribute to worsening respiratory failure in fatal COVID-19.

pagepress

CO112

DEVELOPING AN *IN VITRO* MODEL TO ANALYZE PLATELET-ENDOTHELIAL INTERACTIONS UNDER DIABETIC AND INFLAMMATORY CONDITIONS

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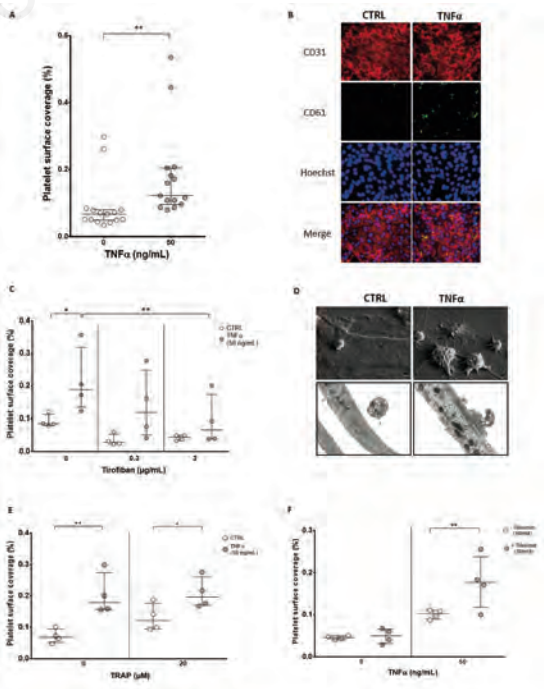
Background and Aims: The endothelium provides an antithrombotic barrier that promotes normal blood flow, but alterations of the endothelial balance can lead to vascular disease. While several pathological conditions, including inflammation and hyperglycemia, are known to impair endothelial-platelet interactions, comprehensive models to study these interactions under controlled yet complex pathological conditions are lacking. The aim of our study was to set up an *in vitro* model to examine the dynamics of platelet adhesion to endothelial cells under conditions that mimic endothelial inflammation and metabolic dysfunction, such as observed in diabetes.

Methods: Primary human aortic endothelial cells (HAECs) were cultured and subjected to pro-inflammatory and hyperglycemic conditions. Specifically, HAECs were stimulated with TNFα (50 ng/mL) to induce cell inflammation, and/or with high glucose levels (30 mM) to mimic hyperglycemia. HAECs were then labelled with Cell Tracker™ Orange and exposed to hirudinated platelet-rich plasma from healthy volunteers (n=21). Samples were then washed with Hank's buffer (HBSS) and fixed with paraformaldehyde. Adhering platelets were labelled with FITC anti-human CD61 and visualized with a fluorescence microscope. To enhance the cellular contrast, in some experiments, HAECs were also stained with anti-CD31 antibody followed by a secondary antibody. In other experiments, platelets were pre-treated with tirofiban or activated with TRAP (Thrombin Receptor Activating Peptide) prior to exposure to HAECs. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were used to analyse the ultrastructure and morphological characteristics of platelets during adhesion.

Results: TNFα-treated HAECs demonstrated a statistically significant increase in platelet adhesion compared to untreated HAECs, with notable platelet morphological changes such as pseudopodia formation and granule release, indicative of platelet activation as visualised and analysed by fluorescence microscope, SEM and TEM (Figure 1A-1B, 1D). Inhibition experiments with tirofiban revealed a decrease in platelet adhesion in both untreated and TNFα-treated HAECs (Figure 1C), underscoring the role of glycoprotein IIb/IIIa in mediating these interactions. Moreover, platelets pre-activated with TRAP showed increased adhesion to untreated HAECs, but not to TNFα-stimulated HAECs, suggesting a saturation or modification of adhesion dynamics under inflammatory conditions (Figure 1E). Finally, while high glucose alone did not alter platelet adhesion, its combination with TNF-α increased adhesion (Figure 1F), highlighting a synergistic effect of metabolic and inflammatory stressors on endothelial-platelet interactions.

Conclusions: Our findings confirm that inflamed endothelium significantly promotes platelets adhesion and activation, effects that are amplified under hyperglicemic conditions. Furthermore, our results suggest that endothelial dysfunction is a primary driver of platelet adhesion, exerting a more significant influence than platelet activation itself. Our *in vitro* model effectively mimics complex pathological states and offers a valuable tool for dissecting the mechanisms of platelet-endothelium interaction. This model could facilitate the development of targeted interventions aimed at mitigating thrombotic risks associated with endothelial dysfunction in various diseases, including diabetes and cardiovascular disorders.



(A) Platelet adhesion on HAECs treated without and with TNFα (50 ng/mL) (n=15). (B) Fluorescence microscopy representative images (40X) of platelet adhesion on HAECs: HAECs are labelled with anti-CD31 antibody (red), platelets are labelled with FITC anti-human CD61 (green) and nuclei are stained with Hoechst (blue). (C) Adhesion of platelets pre-treated with tirofiban on HAECs. (n=4) (D) TEM and SEM representative images of platelets adhesion and activation. (E) Effect of TRAP-preactivated platelets and (F) high glucose levels on platelet adhesion (n=4). Data are shown as median percentage of adhering platelets ± interquartile ranges.

Figure 1.

CO113

DECREASED EXPRESSION OF THE TP ISOFORM OF THE THROMBOXANE A2 RECEPTOR ALTERS ENDOTHELIAL CELL FUNCTION

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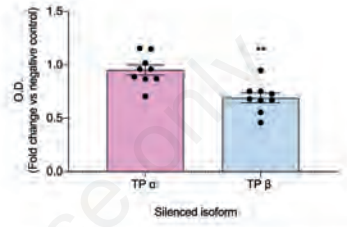
Background and Aims: TXA_2 is a product of AA metabolism and is generated by activated platelets by the sequential action of phospholipase A_2 ($cPLA_2$), cyclooxygenase-1 (COX-1) and thromboxane synthase (TXS). TXA_2 acts in an autocrine and a paracrine manner by activating two T-Prostanoid receptor (TP) isoforms, expressed respectively by the placenta (TPα) and the endothelium (TPβ). Both isoforms are encoded by the TBXA2R gene through alternative splicing, share an identical N-terminal but have a different C- terminal tail. Heterozygous mutations of *TBXA2R* cause TP receptor deficiency, an inherited mucocutaneous bleeding disorder for which only 6 genetic variants have been described so far. While it is well established that TPβ is crucial for endothelial function, the impact of genetic mutations of the TP receptor on the endothelium is unknown. TP receptor activation is known to trigger human endothelial cell migration and angiogenesis (PMID: 10623605), but the specific role of the two isoforms is debated, with studies describing TPβ as an inhibitor of migration, proliferation and angiogenesis (PMID: 18802021, PMID: 14963009), and as an apoptotic inductor (PMID: 11055976) and other studies showing that stimulation of TPβ promotes migration and invasion (PMID: 18519668). Impaired angiogenesis might contribute to hemorrhage, given that angiogenesis inhibitors cause bleeding (PMID: 20434006). In our Center we have characterized a patient with a bleeding history and a TP receptor defect caused by a genetic variant affecting the alternative splice site for TPβ (g.A11765T) leading to the loss of 50% of TPβ. Aim of our study was to shed light on the pathogenesis of TP-receptor deficiency by elucidating the role of TPβ in endothelial cell function.
Methods: Specific siRNA molecules were designed to selectively silence TPα or TPβ in endothelial colony forming cells (ECFCs) differentiated from peripheral blood of healthy controls. ECFCs were differentiated from peripheral blood of the patient with the g.A11765T *TBXA2R* variant and were characterized by flow cytometry from passage 2. Proliferation was assessed by a EdU-based cell proliferation assay in cells from passages 2 to 8.
Results: ECFCs from controls expressed the typical endothelial markers (CD31, CD146, CD309), near to 10% of ECFCs expressed the hematopoietic progenitor cell antigen (CD34), ECFCs did not express the monocyte and leukocyte markers (CD14, CD45). Patient ECFCs after 3 passages showed a proliferation defect and died without the possibility to characterize them or carry out any other experiment. This happened in three different occasions. We identified 2 siRNA molecules able to selectively silence TPα or TPβ. ECFCs in which TPα was silenced incorporated EdU comparably to ECFCs transfected with the negative control siRNA, while ECFCs in which TPβ was silenced incorporated significantly less EdU, thus indicating impaired proliferation (Figure 1) in line with reduced cell proliferation that we observed in ECFCs cultured from the patient with the TP-receptor defect.
Conclusions: Our results suggest a major role of TPβ in endothelial cell proliferation and survival, therefore gene variants in TPβ might have an impact on endothelial cell function. Impaired proliferation might contribute to the hemorrhagic tendency of patients with the TP-receptor deficiency.



Legend to Figure 1. *Cell proliferation of ECFCs as assessed by EdU incorporation. Data are shown as relative fluorescence intensity respect to ECFCs not incubated with EdU. n=10 for negative control (NC) and n=9 for ECFCs in which TPα or TPβ was silenced **p<0.01 vs NC; Student's t-test.*

Figure 1.

CO114

DEVELOPING A 3D BLOOD VESSEL-ON-CHIP MODEL OF THROMBOSIS

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Background and Aims: Thrombosis, a significant contributor to the global disease burden, is governed by the intricate interplay among endothelial cells (EC), platelets, and blood coagulation factors. Understanding the fundamental molecular mechanisms holds paramount importance in the advancement and management of anti-thrombotic therapies. However, the majority of current *in vitro* assays lack the inclusion of EC. Here, we developed a vessel-on-chip model of thrombosis that recapitulates the main components of haemostasis, including EC, blood factors, blood cells, extracellular matrix and shear stress.
Methods: Employing a needle-based fabrication technique, we created a hollow cylinder (300 µm diameter; 5 mm length) embedded within a collagen matrix (based on [1]). Human umbilical vein EC (HUVEC)

were seeded and cultured within the channel for 3-5 days until achieving a confluent monolayer, validated via immunostaining for DAPI and VE-cadherin. Continuous monodirectional perfusion was enabled by a custom, optically-accessible reservoir unit, ensuring media turnover, exerting shear stress on the cells lower than 0.3 dyn/cm2. Permeability was assessed as readout of vessel integrity by 70 kDa TRITC-Dextran diffusion test, coupled with time-lapse imaging over 20 min.
Results: To investigate thrombosis, whole blood from healthy donors was perfused through the EC-lined vessels over a 20-minute interval. Platelets were labelled with PE-labelled CD41 antibody and Alexa Fluor 647-conjugated fibrinogen was added to the blood sample to visualise fibrin. Platelet deposition and fibrin formation were quantified via image analysis and time-lapse microscopy. Endothelial activation with TNF-α (10 ng/ml, 4 hr) led to increased platelet adhesion and fibrin deposition compared to control vessels, as expected. Endothelial activation was corroborated by qRT-PCR, revealing upregulation of adhesion molecules ICAM-1 and E-selectin and of pro-coagulant tissue factor (TF). Thrombus formation was inhibited by an anti-TF antibody. In pursuit of a personalized thrombosis model, endothelial colony forming cells (ECFC) from healthy donors [2] were also used. Platelet adhesion and fibrin deposition exhibited results comparable to HUVECs, underlining the feasibility of the approach.
Conclusions: In conclusion, we have engineered a perfused thrombosis model encompassing all key elements of thrombus formation, including EC. The model offers flexibility to independently manipulate multiple variables relevant to thrombus formation within a 3D vessel structure and to include patients' own cells and blood for personalised studies.

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CO115

FACTOR VIII IS A REGULATOR OF ANGIOGENESIS AND A PROMOTER OF ENDOTHELIAL BARRIER STABILITY

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Background: Haemophilia A (HA) is a rare bleeding disorder caused by the absence or dysfunction of factor VIII (FVIII). The main clinical manifestation is spontaneous bleeding, but an attenuated microvascular endothelial functionality was also observed in HA patients, suggesting an altered homeostasis of endothelial cells (ECs).
Aims: To elucidate the effect of several rFVIII concentrates on the maintenance of EC functionality and stability.
Methods: Blood outgrowth endothelial cells (BOECs) were isolated from HA patients and healthy donors. HA BOECs were treated *in vitro* with simoctocog alfa, efmoroctocog alfa, rurioctocog alfa pegol, damoctocog alfa pegol, or octocog alfa. EC functionality was evaluated *in vitro* by tubulogenic, migration, permeability and proliferation assays. The binding of rFVIII to BOEC membranes was assessed by TriCEPS technology. *In vivo*, the impact of the different rFVIII concentrates was evaluated in NOD/SCID γ–Null HA (NSG-HA) mice with a permeability assay by Evans Blue dye injection.
Results: Impaired tubulogenesis, migration and permeability of HA ECs *vs* healthy ECs were observed. A significant enhancement of EC functionality was demonstrated by treating HA BOECs with rFVIII products, with a higher positive effect for simoctocog alfa. Moreover, in NSG-HA mice treated with different rFVIII concetrates, and subsequently injected with Evans Blue dye, we showed a significant reduction of dye extravasation with a complete correction in mice treated with simoctocog alfa compared with other rFVIII products. Interestingly, we demonstrated that simoctocog alfa can bind to ECs surface triggering the effect on ECs functionality.
Conclusions: Information about the possible extra-coagulative role of FVIII may be crucial to understand the key molecular targets responsible for the impaired EC functionality observed in HA patients. Knowledge of the possible effects of different rFVIII products on EC function may contribute to optimisation of therapeutic approaches for HA patients.

Poster

PO001

MYELOPROLIFERATIVE NEOPLASMS ASSOCIATED WITH USUAL SITE THROMBOSIS: MOLECULAR AND HISTOPATHOLOGICAL FEATURES

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Background and Aims: Myeloproliferative neoplasms (MPNs) associated with thrombosis at unusual sites (UST) present distinct clinical features, particularly splanchnic vein thrombosis (SVT), necessitating comprehensive interdisciplinary collaboration. This study aims to characterize the molecular landscape of MPN-UST using NGS and correlate it with clinical, histological features, and prognosis.
Methods: We retrospectively reviewed clinical-morphological data and analyzed mutational profiles using NGS in 44 consecutive MPN-UST patients admitted to Hematology Units at AOU delle Marche and Pescara between July 1992 and November 2020.
Results: At the time of thrombosis, we identified PV in 22.7%, ET in 20.5%, PMF in 31.8%, SMF in 9.1%, and MPN-U in 15.9% of cases. Concurrent diagnosis of MPN and thrombosis occurred in 50% of cases. Most cases (86.4%) harbored the JAK2V617F mutation, with other molecular markers including CALR mutations in four cases and MPL in one. Additional mutations were frequently found in TET2 (22.7%) and KIT (18.1%) genes. Cases with JAK2V617F homozygosity had a higher median number of additional mutations than those with low allele burden. However, no significant difference was observed in thrombotic recurrence, fibrotic or acute progression, or mortality between cases with and without additional somatic mutations. Pathologically, most patients exhibited an early phase of thrombosis characterized by increased megakaryocytes, altered megakaryocyte sizes, nuclear/cytoplasmic atypia, and a tendency to form clusters. U2AF1 was associated with advanced fibrosis stages, while ASXL1 correlated with early fibrosis stages and increased megakaryocytes without cellular atypia. Patients with KIT mutation tended to lack megakaryocyte clusters. Leukemic evolution was observed in 2 cases, and 8 cases progressed to myelofibrosis. After a median follow-up of 8.7 years, nine deaths were recorded, with age at diagnosis and MPN type significantly influencing overall survival (OS). In univariate analysis, absence of TET2 mutation, constitutional symptoms, and hemoglobin and platelet count at diagnosis were significant predictors of OS (Figure 1).
Conclusions: NGS plays a pivotal role in managing MPN-SVT, aiding in diagnosis confirmation, and providing insights into disease prognosis.

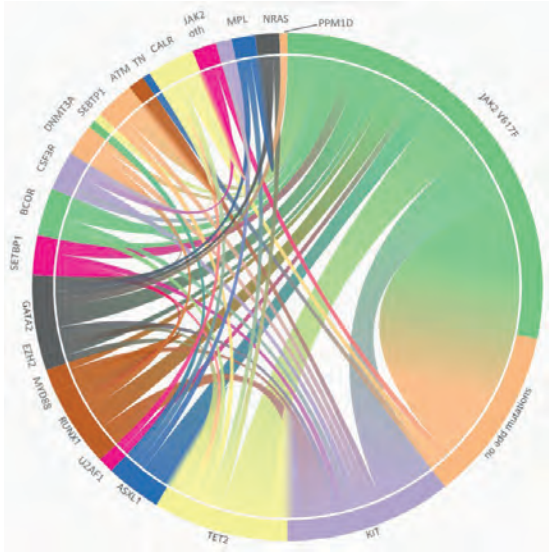

Figure 1.

PO002

DIFFERENCES IN CLINICAL AND MOLECULAR PROFILES AMONG MYELOPROLIFERATIVE NEOPLASMS PATIENTS WITH VENOUS THROMBOSIS IN USUAL AND UNUSUAL SITES

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Thrombosis, including involvement of unusual sites such as the splanchnic veins (SVT), remains a significant cause of morbidity and mortality in myeloproliferative neoplasms (MPN). Currently, there are no known markers to predict whether a patient will experience a venous vascular event in a usual or non-usual site. This study aims to identify differences among patients with MPN who experience post-diagnosis or at-diagnosis venous thrombosis, whether in a usual or non-usual site. We conducted a retrospective cohort study at the MPN units of AOU delle Marche in Ancona and S. Spirito Hospital in Pescara. Unusual site thromboembolism (UTE) includes splanchnic, cerebral, and retinal thrombosis. We collected 59 MPN-UTE cases and compared them with 56 control MPN-VTE cases, matched for sex. Among the MPN-UTE cohort, 43 presented with SVT, 13 with CVT, 2 with retinal vein thrombosis, and 1 with upper limb thrombosis. In the control cohort, 43 patients presented with DVT, 9 with PE, and 4 with superficial thrombophlebitis (ST). Patients with MPN-UTE were younger at diagnosis (median 49 *vs.* 68 years; p <0.0001) and at the time of thrombosis (median 51 *vs.* 72.5 years; p <0.0001) compared to controls. MPN-UTE patients showed a higher prevalence of MPN-U (13.6% *vs.* 1.8%, p=0.0157) and splenomegaly (71.2% *vs.* 30.4%, p <0.0001). JAK2V617F mutation was highly prevalent in MPN-UTE (83.1% *vs.* 55.3%, p=0.0029), while other cardiovascular risk factors were less common (30.5% *vs.* 50%, p=0.0441). More MPN-UTE patients had thrombosis at diagnosis compared to controls (50.8% *vs.* 21.4%, p=0.0009). Thrombotic recurrence rate was lower in MPN-UTE patients (1.2 per 100 patient-years) compared to controls (1.8 per 100 patients-years, p=0.0484). MPN-UTE patients exhibited a more benign clinical course, with a higher survival rate (86.4% *vs.* 67.8%, p=0.0163) and reduced progression to MF or AML (15.3% *vs.* 28.6%, p=0.0498) at the last follow-up. Treatment with cytoreductive therapy did not differ between the cohorts (66.1% *vs.* 76.7%, p=0.5828). Patients with MPN-SVT preferred VKA (55.9% *vs.* 28.8%) compared to those with MPN-VTE, who were primarily treated with DOACs (16.9% *vs.* 39.3%, p=0.0035). Our study demonstrates that MPN-SVT presents clinically and molecularly distinct characteristics compared to MPN with thromboses in usual sites. Additionally, it indicates a more indolent course, leading to better survival and fewer thrombotic recurrences (Figure 1).

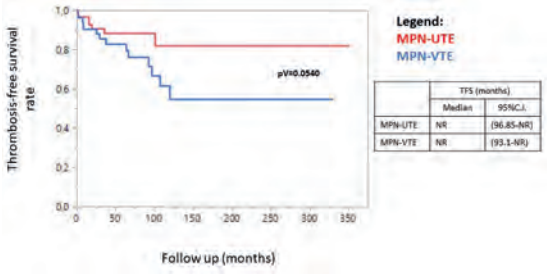

Figure 1.

PO003

TUMOR THROMBUS OR MESENTERIC VEIN THROMBOSIS? ISSUES ABOUT DIAGNOSIS, TREATMENT CHOICE AND THE ROLE OF FDG-PET IN A NEOPLASTIC PATIENT

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Background: Tumor thrombus is defined as a tumor extenting into a vessel, tipically a vein. It occurs in a wide variety of malignancies, especially renal and epatic cancers. It is usually composed of a soft malignant tissue material mixed with thrombotic componenent. In a neoplastic setting, it is essential to distinguish tumor thrombus from "bland" thrombus, tipically free of cancer cells, as it presents distinct impacts on treatment and prognosis. Differently from thrombosis, the main managment of tumor thrombus is generally surgical or chemo-pharmacological. Both MRI and CT have high accuracy in detecting tumor thrombus and distinguishing it from bland thrombus. Therefore, tumor thrombus could be better differentiated from benign trombus on the basis of major enhancement and uptake at FDG-PET, so affetting the approach. Regarding mesenteric venous thrombosis, a local clot impairs the venous return of the bowel. It can be idiopatic, commonly associated with coauglation disorders, or secondary to underline disease or risk factor, generally neoplastic. Consequently, it can led to venous engorgement or mesenteric ischemia, representing a potential life-threatening condition. Splanchnic thrombosis has rarely been addressed in literature. Several studies, based upon evidences on efficacy and safety of antithrombotic therapy, suggest the use of LMWH or reduced-dose DOACs, especially rivaroxaban, but there is not yet an approved consensus treatment. However, use of DOACs, although considered, is currently off-label.

Case Report: A 73-year-old woman was diagnosed with cecum mucinous adenocarcinoma and underwent

right hemicolectomy in last Jenuary. She did not present metasteses at diagnosis. After two months, she was admitted to ER for vomit and diarrhea and hospitalized in an internal medical setting. A fews days before, she took an abdominal CT-scan that showed the presence of a nodular spiculeted mass incorporating and infltrating a great part of mesenteric vein with a volominous thrombotic lesion extended to portal and hepatic system. She did not have severe alterations in blood count, inflammation and tumor markers. Stool cultures resulted negative. She was treated with antibiotic therapy and rehydration with rapid symtomps disappear. In order to understand the nature of the abdominal mass and discriminate it from a neoplastic relapse, she has undergone a FDG-PET that did not reaveal the appearence of malignant lesions or intense abdominal uptake, suggesting the presence of benign acute thrombosis without tumor thrombus. After an oncological evaluation, she started adjuvant therapy and antithrombotic treatment with enoxaparin, excluding the need of a surgical managment. The issues on drug choice were related to patient's hesitation for an off-label medication, blooding risks and chemotherapy interactions.

Conclusions: The appropiate treatment of mesenteric thromboembolism is still a reaserch topic without shared guidelines. It is vital to distinguish tumor thrombus from bland thrombus, especially in abdonimal neoplastic setting, as this often impacts staging and treatment approach. Our case demonstrated the role of FDG-PET in dectecting active tumor thrombosis and its importance in differentiating benign thrombous from tumor thrombus, so to avoid any unnecessary, invasive and costly procedures or surgery. Further investigations are essential to find the most effective treatment strategy of mesenteric vein thrombosis.

PO004

PREVALENCE OF OCCULT CANCERS DETECTED BY COMPUTED TOMOGRAPHIC PULMONARY ANGIOGRAPHY IN PATIENTS HOSPITALIZED FOR ACUTE PULMONARY EMBOLISM

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Background: Acute pulmonary embolism (PE) can occur as a manifestation of an underlying cancer and be of paraneoplastic etiology. Ten per cent of patients with unprovoked VTE will be diagnosed with cancer within the next 12 months. A previously unknown cancer is sometimes diagnosed at the acute PE diagnosis, during standard imaging evaluation with computed tomographic pulmonary angiography (CTPA).

Aim: The aim of our study was to evaluate the prevalence of previously unrecognized malignancy at the time of the acute PE presentation.

Methods: We studied consecutive patients admitted to the Internal Medicine Department of Moscati hospital Avellino from January 2024, for acute PE, diagnosed with CTPA. The patients were studied with routine laboratory evaluation, thrombophilia, and complete vascular Doppler ultrasound.

Results: Twenty-five patients (female:11, male:14) were included in the study. The mean age was 64.82 years. Patients with a known previous cancer diagnosis were excluded from the analysis. The CTPA evaluation, in 8/25 (32%) patients, revealed abnormalities suggestive of previously unknown cancer (and further investigations revealed 2 lung cancers, 2 gastrointestinal, 1 liver cancer, 2 ovarian cancers and 1 prostatic cancer). Six out of 25 patients (24%) were positive for thrombophilia, 2/25 (8%) were positive for antiphospholipid antibody syndrome, 8/25 (32%) were affected by deep vein thrombosis (DVT), 3/25 (12%) were in antiplatelet therapy, only 1/25 (4%) was in anticoagulant therapy, 2/25 (8%) are deceased.

Conclusions: Our study shows that 32% of patients hospitalized for acute PE in an Internal Medicine Department are diagnosed with previously unknown cancer at the time of PE diagnosis. These data are contrasting with lower previously reported frequencies and underline the ever-increasing incidence of cancer in the population examined for acute PE.

PO005

THROMBOEMBOLISM PROPHYLAXIS WITH LONG-TERM REDUCED-DOSE DOAC IN CANCER PATIENTS: SINGLE-CENTER EXPERIENCE

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Background: Risk of venous thromboembolism (VTE) is 4 to 6-fold increase in cancer patients (pts). For these pts guidelines suggest long-term anticoagulation for secondary prophylaxis using low molecular weight heparin (LMWH), dicumarolics or direct oral anticoagulants (DOAC). Retrospective studies and randomized trials showing that DOAC appears to be as effective and safe

as LMWH, also in long term utilization, in the treatment of VTE in cancer pts are published. In contrast, fewer data are available for secondary prophylaxis in cancer pts using reduced-dose DOAC.

Methods: Data on an oncological subgroup of pts with VTE history treated in secondary prophylaxis with reduced-dose DOAC (rdDOAC) between April 2017 and March 2024 was retrospectively collected and analyzed.

Results: A total of 110 oncological pts were treated with rdDOAC in secondary prophylaxis; 70 pts received rivaroxaban 10mg/d (rivaroxaban group; Rg) and 40 pts received apixaban 2.5mg BID (apixaban group; Ag). Median observation period in rdDOAC was 26.6 months in Ag and 17.6 months in Rg. Characteristics of population are summarized in Table 1. Central venous catheter-related thrombosis was first VTE event in 13/110 pts. During rdDOAC 9 pts had a VTE event; 4 pts (10.5%) in the Ag and 5 pts (7.14%) in the Rg. 7/9 had an additional thrombotic risk factor. Recurrence was observed in pts with colorectal carcinoma (2), hematological malignancies (2), breast cancer (2), astrocytoma (1), prostate adenocarcinoma (1) and carcinoma of the oropharynx (1). The median duration of prophylaxis at time of event was 13 months (IQR 10,5-18,5) in the Ag and 12 months (IQR 11-28) in the Rg. At 12 months, 6.7% of pts in Ag and 6.5% in Rg experienced a VTE event. During rdDOAC 11 pts had a hemorrhagic event; 3 pts (8.11%) in the Ag and 8 pts (11.4%) in the Rg. Six of 11 pts had an additional hemorrhagic risk factor. Neither major bleeding was recorded nor discontinuation of therapy was needed.

Conclusions: in our experience the use of DOAC at reduced dosage in order to prevent recurrence of VTE in cancer pts has been shown to be safe and effective without significant difference between the two drugs. Equal VTE recurrence rate between Ag and Rg was observed. Our cohort shows a comparable recurrence rate of VTE than in studies of full-dose DOACs in cancer patients with lower risk of bleeding and longer follow-up available.

Table 1.

	Apixaban (A) N=40	Rivaroxaban (R) N=70	p.overall
Age at last VTE (years)	71.6	67.5	0.067
Male	26 (65.0%)	32 (45.7%)	
BMI > 30	1 (2.50%)	6 (8.57%)	0.419
Mean number of previously TEV	0.75	0.63	0.498
Follow-up in rdDOAC (months)	26.6	17.6	
Thrombophilia	9 (22.5%)	7 (10.0%)	
Median time in full dose anticoagulation before rdDOAC (months)	18.0	21.0	0.544
Bleeding during rdDOAC	3 (8.11%)	8 (11.4%)	**0.744**
Median time in rdDOAC at bleeding event (months)	16.3	18.0	0.885
VTE events in rdDOAC	4 (10.5%)	5 (7.14%)	**0.717**
Median time in rdDOAC at TEV event (months)	13	12	0.019
Status at last Follow-up visit:			
Alive	29 (72.5%)	52 (74.3%)	
Death	11 (27.5%)	17 (24.3%)	
Lost at follow-up	0 (0.00%)	1 (1.43%)	

PO006

PROSPECTIVE EVALUATION OF THROMBO-HEMORRHAGIC EVENTS AND HYPERCOAGULATION BIOMARKERS IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA RECEIVING INDUCTION THERAPY

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Background and Aims: A typical life-threatening coagulopathy, secondary to TF-mediated clotting activation, characterizes the onset of acute promyelocytic leukemia (APL). Current protocols including arsenic trioxide (ATO) and all trans retinoic acid (ATRA) have exhibited beneficial effects on the hemostatic imbalance, particularly downregulating cellular TF expression. However, the rate of early deaths due to the thrombo-hemorrhagic syndrome is still relevant. Therefore, characterizing the coagulopathy and identifying predictive markers remains a critical issue. In the present study, we prospectively recorded thrombo-hemorrhagic (TH) events occurrence in the first month after APL diagnosis, and monitored the circulating hypercoagulation markers and the molecular expression of TF, before and during induction therapy.

Methods: Sixty-five consecutive APL patients receiving ATRA+Idarubicin (n=60, GIMEMA AIDA2000) or ATRA+ATO (n=5, GIMEMA APL0406) for remission induction were enrolled in 2 Italian Centers (2005-2015). Blood samples from a subgroup of 35 patients were obtained at diagnosis before therapy (D0), and during induction on days (D)7, 14 and 28, and tested for Tissue Factor mRNA (TF mRNA) expression by peripheral mononuclear cells (PBMC) and for plasma levels of FVII-Antithrombin Complex (FVIIa-AT), a parameter of TF activity, together with markers of thrombin generation (Thrombin-Antithrombin complex, TAT) and fibrinolysis (D-dimer).

Results: At D0, 12 patients (18%) presented with TH events: 8 major bleeding (3 fatal intracranial and 5 non-fatal major bleedings (MB) and 4 thrombosis (1 fatal). Within 3 days of ATRA, 2 additional fatal intracranial bleedings occurred, accounting for 9% early deaths. In the next 20 days, 3 non-fatal MB and 2 non-fatal thrombosis developed. The laboratory showed that, at D0, the plasma levels of FVIIa-AT, TAT and D-dimer were significantly higher in APL patients compared to controls. During induction therapy, the levels of TAT and D-dimer significantly and progressively decreased at D7, and were lowest at D28. Differently, FVIIa-AT levels dropped significantly at D28. In addition, the levels of TF mRNA, significantly higher than controls at D0, during induction therapy were significantly decreased by 68%, 70%, and 90%, at D7, D14 and D28, respectively.

Statistically significant correlations were found between the decrease in TF mRNA and the decrease in FVIIa-AT levels during induction therapy.
Conclusions: Our data show a significant rate of severe thrombo-hemorrhagic events in our cohort of APL patients (19/65, 29%), including 6 early fatal events. Laboratory data demonstrate the TF mRNA downregulation under induction therapy, which parallels hypercoagulation markers decrease. Persistent high TF-dependent clotting activation (FVIIa-AT) might explain post-ATRA TH events. Although the small size of the study did not allow to calculate the predictive value of biomarkers on the occurrence of TH events, our results provide background for a larger evaluation in a wider APL population.

PO007

A RETROSPECTIVE STUDY COMPARING DOACS *VERSUS* ASA AS PROPHYLAXIS OF MAJOR THROMBOTIC EVENTS IN LENALIDOMIDE EXPOSED MULTIPLE MYELOMA PATIENTS

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Background and Aim: Immunomodulatory drugs (*e.g.*, lenalidomide), which are currently the backbone of MM therapy, are strongly associated to venous TE and aspirin (ASA) has been usually administered prophylactically in this setting. However, controversies exist on the actual benefit of ASA, given the still non-negligible rate of TE registered despite its use. A potential alternative strategy would be the recourse to direct oral anticoagulants (DOACs) but data are currently lacking. To gain more insight into this, we studied a cohort of 17 patients with MM undergoing lenalidomide-containing regimens who were given ASA or DOACs as thromboprophylaxis.
Methods: We enrolled 17 MM patients diagnosed and treated at Policlinico Tor Vergata of Rome (Italy). Choice of prophylaxis was based on prior history of TE, patient's compliance, and TE risk evaluated using IMPEDE and SAVED scores. Incidence of major TE during treatment and bleeding related to thromboprophylaxis were evaluated according to the ISTH BATH score.
Results: Overall, the median age of our cohort was 73 years (range 59–78) with a 3.25 M/F ratio., Nine patients had a history of previous TE and were considered eligible for low molecular weight heparin (LMWH) but, due to poor compliance, shifted to DOACs. The rest of the patients (n=8) were given ASA. Among ASA-exposed patients, 25% qualified as low risk (≤3), 75% as intermediate (4-7), and none as high risk (≥8), according to the IMPEDE score. Among DOACs-exposed patients, 33.3% and 66.7% qualified intermediate and high risk, respectively. When reclassifying patients as per the SAVED score, 62.5% of ASA-exposed qualified as low risk (0-1), while the remaining 37.5% as high risk (≥2). Forty-4.4% and 55.6% of DOACs-exposed were at low and high risk, respectively. ASA-exposed patients had an almost 8-fold higher risk to experience an episode of TE than DOACs-exposed patients (p=0.061, hazard ratio 7.57, 95% confidence intervals 0.91-63.06). Furthermore, DOACs-exposed patients achieved a complete vein recanalization whereas 83% of ASA-exposed did the same. With a median follow-up of 16 months, a single episode of bleeding was observed in 1 patient receiving DOACs (ISTH-BATH score 0) whereas no hemorragic event occurred in the ASA group.
Conclusions: Even though in a limited series of patients, we report a trend toward a lower incidence of TE in patients with MM, who are prophylactically exposed to DOACs *vs* ASA. Our cohort presented a higher thrombotic risk, assessed according to commonly used risk scores, and already suffered from previous TE. Our study provides preliminary evidence of the safety profile and potential advantage of DOACs given as thromboprophylaxis in MM patients receiving lenalidomide, paving the way to studies exploring further this subject.

PO008

LONG-TERM FOLLOW-UP OF PATIENTS WITH MYELOPROLIFERATIVE NEOPLASM-ASSOCIATED SPLANCHNIC VEIN THROMBOSIS (MPN-SVT): A COMPARATIVE ANALYSIS BETWEEN TWO DIFFERENT COHORTS

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Background and Aims: MPN-SVT is a unique condition requiring interdisciplinary collaboration for diagnosis and management. While emerging data suggest the potential benefit of direct oral anticoagulants (DOACs) as a first choice of treatment in MPN-SVT, real-world practice data in this context are currently lacking. This study aimed to describe the clinical and biological features of MPN-SVT, management, and long-term outcomes in two cohorts. In a subsequent analysis including a larger cohort, we aim to assess the risk of recurrences and the evolution of the underlying MPN, while also evaluating the effectiveness of current anticoagulation strategies.
Methods: A total of 85 patients diagnosed with MPN-SVT referred to Guy's Hospital (UK) were retrospectively analysed in this study and compared to an Italian cohort of 55 MPN-SVT patients.
Results: The two cohorts of 85 and 55 patients with MPN-SVT were analysed in a median follow-up time of 7.7 years and 8.1 years, respectively (p=0.73). Patients from the UK cohort were younger at the time of the MPN diagnosis than those from the Italian group (median age 44 years *vs.* 52, p=0.038). In the UK cohort, MPN and

SVT diagnoses coincided in 56 patients (65.9%), while in the Italian cohort, the two diagnoses coincided in 29 patients (52.7%). The portal vein was the most common site of thrombosis in both cohorts. No significant differences were found when comparing the two groups based on the presence of single or multiple sites of thrombosis (p=0.07). Polycythaemia Vera was the most frequent MPN-SVT subtype in the UK cohort differently from the Italian cohort (63.5% *vs.* 23.6%, p<0.001) where Essential Thrombocythaemia was the prevalent diagnosis (32.7%). Driver mutation frequencies were not significantly different between the cohorts. All the main clinical and laboratory findings of the two cohorts of MPN-SVT patients are reported in Table 1. Next-generation sequencing (NGS) analysis was performed on 26 (30%) patients from the UK cohort and showed additional mutations in 7 (27%) cases, whereas was available in 39 (70%) patients from the Italian cohort where 18 (46%) of those showed the presence of additional mutations. After the diagnosis, most patients from both cohorts (70% *vs* 75%, p=0.73) were prescribed vitamin K antagonists (VKAs). In 17 patients (20%) of the UK cohort, DOACs were used as the first choice, and one patient of the Italian cohort. At the last follow-up, 47% of UK patients were on DOACs, and 11% of Italian patients had shifted from VKAs. No differences were found in thrombotic recurrence incidence between the cohorts (p=0.32), while major hemorrhage incidence was significantly higher in the UK cohort (24% *vs.* 7.3%, p=0.009). The overall survival (OS) at the last follow-up was 89.4% *vs.* 76% in the UK and Italian cohorts, respectively. Finally, the median OS was not significantly different across the two cohorts (29.8 years *vs* 27.9 years, p=0.30).

Table 1.

Clinical and laboratory findings of two cohorts of MPN-SVT patients.

	GSTT cohort (85)	Italian cohort (58)	*P*
Age at MPN diagnosis (years), median (range)	44 (13-70)	55 (31-79)	**0.038**
Age at SVT diagnosis (years), median (range)	45 (13-75)	57 (17-81)	**0.015**
Gender (M/F), n	35/50	24/34	0.77
MPN subtype, n (%)			
Polycythaemia Vera	54 (63.5)	13 (23.6)	**<0.001**
Essential Thrombocythaemia	11 (12.9)	18 (32.7)	0.05
Primary and Secondary Myelofibrosis	10 (11.8)	17 (31)	0.05
MPN-U	10 (11.8)	7 (12.7)	0.88
Sites of SVT (single/multiple)	29/56	28/27	0.07
Hb at MPN diagnosis (g/dL), median (range)	13.5 (8-20.9)	14 (7.2-21.2)	0.76
Hct at MPN diagnosis, median (range)	44.2 (25-60.4)	44.8 (22.3-65.7)	0.92
WBC at MPN diagnosis (x10^9/L), median (range)	8 (4-41.9)	7.45 (3-16.8)	0.74
PLT at MPN diagnosis (x10^9/L), median (range)	389 (130-1800)	335 (44-1364)	0.14
NLR at MPN diagnosis, median (range)	3.6 (0.8-14.9)	2.95 (0.43-25.4)	0.49
Hb at SVT diagnosis (g/dL), median (range)	13.5 (8-20.9)	14 (7.2-21.2)	0.66
Hct at SVT diagnosis, median (range)	41 (25-57)	39.7 (22.3-65.7)	0.67
WBC at SVT diagnosis (x10^9/L), median (range)	7.2 (4-42)	8.6 (1.15-31)	0.47
PLT at SVT diagnosis (x10^9/L), median (range)	382 (130-1395)	347 (44-1382)	0.35
Constitutional symptoms at MPN diagnosis, n (%)	46 (54.1)	12 (21.8)	**<0.001**
Splenomegaly at MPN diagnosis, n (%)	63 (74.1)	44 (80)	0.42
*JAK2*V617F, n (%)	79 (92.9)	47 (85.5)	0.14
*JAK2*V617F VAF (%), median (range) N evaluable (GSTT/Italian=51/28)	24 (4-91)	20.1 (0.8-89)	0.88
*JAK2*V617F VAF ≥50, n (%)	7 (20)	7 (25)	0.63
CALR, n (%)	3 (3.5)	5 (9.1)	0.16
MPL, n (%)	0 (0)	2 (3.6)	0.07
Triple-negative, n (%)	3 (3.5)	0 (0)	0.15
Exon12, n (%)	0 (0)	1 (1.8)	0.21
CV risk factor, n (%)	62 (72.9)	17 (31)	**<0.001**
Thrombophilia screening available, n (%)	23 (29.4)	42 (78.4)	**<0.001**
At least one thrombophilic risk factor, n (%)	15 (60)	21 (50)	0.05
History of previous thrombosis, n (%)	8 (9.4)	7 (12.7)	0.53
Thrombosis recurrence, n (%)	18 (21.2)	8 (14.5)	0.32
Major Haemorrhages, n (%)	21 (24.7)	4 (7.3)	**0.009**
Anticoagulant therapy, n (%)	83 (98)	52 (94.5)	0.32
VKA as first-line therapy	58 (70)	39 (75)	0.73
LMWH in first-line therapy	8 (9.6)	12 (23)	**0.04**
DOAC in first-line therapy	17 (20.4)	1 (2)	**0.002**
DOAC at the time of the last follow-up	40 (47.1)	6 (11)	**<0.001**
Cytoreduction at the last follow-up, n (%)	81 (95)	52 (95)	0.84
Hydroxycarbamide	29 (35)	35 (67)	**<0.001**
Anagrelide	2 (2.5)	0 (0)	0.25
Peg-Interferon	27 (33)	3 (5.8)	**<0.001**
Ruxolitinib	23 (28.3)	14 (27)	0.83
Myelofibrosis progression, n (%)	13 (37.1)	10 (18.2)	0.05
Leukemic evolution, n (%)	3 (3.5)	1 (1.2)	0.55
Time to progression/evolution (months), median (range)	127 (22-275)	188 (15-300)	0.27
Death, n (%)	9 (10.6)	13 (23.6)	**0.038**
Follow-up from MPN diagnosis (months), median (range)	93 (3-358)	90 (8-417)	0.75

Conclusions: We confirmed a similar phenotype in both MPN-SVT and highlighted, during a relatively long follow-up, the increased use of DOACs in this patient population. The complexity of managing this rare entity was evident in the variation of antithrombotic strategies observed from initial diagnosis to recent follow-up. This underscores the importance of enhancing data availability to identify reliable predictors of vascular events and optimise patient outcomes.

PO009

HEMOSTATIC PARAMETERS AS POTENTIAL BIOMARKERS OF POOR PROGNOSIS IN HEALTHY SUBJECTS WHO DEVELOPED CANCER: PRELIMINARY RESULTS FROM THE HYPERCAN STUDY

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Background and Aims: In most patients with cancer, there is a condition called hypercoagulable state, characterized by a subclinical activation of blood coagulation, whose magnitude is associated with a poorer prognosis. However, in otherwise healthy subjects, the presence of a hypercoagulable state may be the early sign of an occult cancer. This study, in a large cohort of healthy subjects, aims to investigate whether the detection of a hypercoagulable state can predict cancer with a poor prognosis.

Methods: HYPERCAN is a prospective Italian, multicentre observational study that prospectively enrolled, from 2012 to 2022, 10,294 healthy blood donors (72% males; median age: 47 years) who have been followed up every 6 months for cancer occurrence. Incidental cancer cases were ascertained by direct linkage with the hospital discharge form. Blood samples were taken at two different time points: enrolment (T0) and 6-18 months later (T1), along with clinical, hematological, and lifestyle data. Plasma levels of D-dimer (ACL TOP 500, Werfen) and prothrombin fragment 1+2 (F1+2, ELISA, Enzygnost, Siemens) were measured as biomarkers of *in vivo* blood coagulation activation. Statistical analyses were performed with the SPSS Statistics version 21.0 software.

Results: During a median follow-up of 9 years, 338 blood donors developed cancer [236M/102F, median age: 53 (31-68) years]. The most frequent tumor site was breast (33%) in females and prostate (22%) in males, followed by non-melanoma skin (18%) and colon-rectum (9%) cancers. According to histological information, most cancer cases (63%) were diagnosed at stage I or II, while 19% were at stage III and 18% at stage IV. Moreover, 48 patients died during follow-up and 84% of them had stage III-IV cancers. The analysis of hemostatic biomarkers in the cohort of cancer cases showed that at T0, there was a significant (p<0.01) increase in both D-dimer (136±73 *vs* 122±202 ng/mL) and F1+2 (332±267 *vs* 269±273 pmol/L) plasma levels in those cases who did not survive, compared to those who did. Interestingly, this difference was also present when samples were analyzed at T1, with D-dimer levels of 152±80 *vs* 121±67 ng/mL (p=0.017) and F1+2 levels of 284±125 *vs*

264±249 pmol/L (p=0.012), indicating the persistence of the hypercoagulable state. Based on the tumor stage, the levels of F1+2 were significantly higher in the cases with advanced cancer stages (IV), both at T0 and T1. Specifically, at the time of enrolment, F1+2 levels were 221±82 pmol/L for stages I to III, and 292±104 pmol/L for stage IV tumors (p=0.011). At T1, F1+2 levels were 265±201 pmol/L for stages I to III, and 342±96 pmol/L for stage IV tumors (p=0.015). After correcting for age and gender using logistic regression analysis, levels of F1+2 higher than the 75th percentile at T0 were significantly associated with a 4-time risk of mortality (OR=4.176, 95% CI=2.042-8.540, p<0.001).
Conclusions: According to our study, among healthy individuals who later developed cancer, a stronger activation of blood coagulation before cancer diagnosis is associated with a poorer prognosis. This correlation is related to factors such as tumor stage or death.

PO010

PRECHEMOTHERAPY LEVELS OF HEMOSTATIC BIOMARKERS CAN IDENTIFY METASTATIC BREAST CANCER PATIENTS AT HIGHER RISK OF DISEASE PROGRESSION AND MORTALITY DURING CHEMOTHERAPY

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Background and Aims: Even with advancements in breast cancer screening, diagnosis, and treatment, nearly 6-7% of patients continue to be diagnosed with advanced-stage breast cancer. In our previous work within the HYPERCAN study, we have shown the significance of hemostatic biomarkers in identifying breast cancer patients with limited resected disease who are at a higher risk of recurrence during follow-up. However, there is limited data available on the effectiveness of these biomarkers in predicting the prognosis of breast cancer patients with metastatic disease. In a prospective, observational cohort of newly diagnosed metastatic breast cancer patients, we aimed to assess whether hemostatic biomarkers measured before starting any anticancer treatment may predict 6-months DP (6m-DP) and 1-year mortality (1y-mortality).
Methods: Newly diagnosed, metastatic breast cancer patients enrolled in the HYPERCAN study (ClinicalTrials.gov ID#NCT02622815) were analyzed. Plasma samples collected before starting any anticancer treatment were tested for thrombin generation (TG) as a global hemostatic assay, and for D-dimer, fibrinogen, and Fragment 1+2 (F1+2) as biomarkers of *in vivo* blood clotting activation. All patients were strictly monitored for DP and mortality during follow-up. Statistical analyses were performed with the SPSS Statistics (version 21.0).
Results: The study involved 189 metastatic breast cancer patients, with a median age of 59 years were. Within 6 months from enrolment, the cumulative incidence of DP was 21%, with a median time to DP was 99 days (range 64-160). After 1 year, the cumulative incidence of mortality was 17% with a median time to death of 187 days (range 72-294). Patients who experienced DP with distant metastasis had significantly (p=0.024) higher levels of endogenous thrombin potential (ETP) (1,806 nM*min) compared to those with regional and local metastasis or to those who remained DP-free (1,618 nM*min). Patients who died within 1 year from enrolment displayed significantly (p=0.017) higher prechemotherapy levels of D-dimer [454 ng/ml (249-982 ng/ml)] compared to those who were still alive after the same period [239 ng/ml (148-438 ng/ml)]. By Cox regression multivariate analysis, prechemotherapy a value of ETP >1,660 nM*min was identified as an independent risk factor for DP with distant metastasis (HR:1.8, IC 95%: 1.1-2.8; p=0.015). Additionally, prechemotherapy levels of D-dimer >300 ng/ml emerged as independent risk factors for 1y-mortality (HR: 3.6, IC 95%: 1.5-8.7; p=0.004).
Conclusions: In a study of metastatic breast cancer patients, we found that pre-chemotherapy levels of ETP and D-Dimer can help identify individuals at higher risk of 6-month or 1-year mortality after starting chemotherapy. These correlations underscore the potential use of these biomarkers in screening programs for disease prevention.

PO011

EVALUATION OF ERYTROCYTE-RELATED PARAMETERS IN HEALTHY SUBJECTS AS PREDICTORS OF CANCER

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Background and Aims: Recent studies have highlighted that abnormal erythrocyte parameters, including red blood cell distribution width (RDW) and mean corpuscular volume (MCV), are frequently observed in cancer patients. There is currently no available information on the role of these abnormalities in cancer risk. In a prospective Italian observational cohort of healthy subjects, we aimed to 1) evaluate the predictive value of MCV and RDW for cancer diagnosis, and 2) understand the possible influence of lifestyle habits on these parameters.
Methods: During a median follow-up of 9 years of the HYPERCAN cohort (N=10,261 blood donors, enrollment 2012-2022), 286 cancer cases were identified. Cases with a cancer diagnosis within 6 months from the enrollment were excluded. A case-cohort study was therefore designed to compare these cancer cases with randomly selected controls from the same cohort. Lifestyle habits (*i.e.* alcohol intake, smoking habits, and sport practice) were collected by a questionnaire administered at the entry into the study. Clinical, hematological, and biochemical data were collected together with blood samples at enrollment and after 6-18 months. Results were expressed as median and 5th-95th percentile range. Statistical differences between groups were tested by the Mann-Whitney test. Multivariable logistic regression analysis was performed to examine the association of covariates with cancer diagnosis. Analyses were performed with the SPSS Statistics version 21.0 software.
Results: The cohort consisted of 1,134 subjects, 286 of them were cancer cases (69% male; age 31-67 years) and 848 were controls (73% male; age 27-68 years). Among cancer cases, the most common tumor site was prostate (25%) in males, and breast cancer (37%) in females. The analysis of hemocromocytometric parameters measured at enrolment showed that MCV ($p<0.001$) and RDW ($p<0.05$) values were significantly higher in cancer cases compared to controls, while among biochemical parameters, levels of cholesterol were significantly ($p<0.05$) elevated in cancer cases compared to controls. In addition, a positive correlation was found between MCV and smoking habits. By multivariate regression analysis, high MCV levels (OR 1.080; 95% CI: 1.031-1.130; p=0.001), high RDW values (OR 1.409; 95% CI: 1.160-1.712; p=0.001) and older age (OR 1.076; 95% CI: 1.052-1.100; $p<0.001$) were found significantly associated with cancer diagnosis. In particular, according to specific cut-off values obtained by ROC analysis, subjects with MCV greater than 87.75fL, RDW higher than 13.45%, and older age had approximately 1.8-fold higher risk of receiving a cancer diagnosis during follow-up (OR 1.839; 95% CI:1.153-2.931; p=0.011). A subgroup analysis performed within the most prevalent tumor in males (prostate) and females (breast), showed a significant positive association between MCV values and prostate cancer diagnosis (p=0.027), and between RDW and breast cancer diagnosis (p=0.014).
Conclusions: Our data provides valuable insights into the potential use of erythrocyte-related parameters for early cancer diagnosis. Moreover, this analysis also draws attention to the positive association between MCV and smoking habits, a well-known modifiable risk factor for cancer, which highlights the significance of adopting a healthy lifestyle in reducing the risk of developing cancer.

PO012

ACTIVATION OF COAGULATION FACTORS AND IMPAIRED FIBRINOLYSIS IN CHOLANGIOCARCINOMA

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Background and Aims: Venous thromboembolism (VTE) which includes deep vein thrombosis and pulmonary embolism, is the most common presentation of the cancer-associated hypercoagulable state. However, in some malignant diseases such as cholangiocarcinoma (CCA), the risk of VTE and the role of the tumor cell in the abnormal activation of the blood coagulation cascade are underestimated. Recent evidence indicate that various components of coagulation pathways are implicated in carcinogenesis and dissemination of tumor cells and their expression correlates with clinical outcome of cancer patients. CCA, an aggressive cancer with still limited therapeutic options, is associated with a gloomy outcome, which may also be affected by the occurrence of VTE. Therefore, in an attempt to better understand the risk of VTE in CCA, our purpose is to define the expression of components of coagulation and fibrinolysis pathways in CCA samples.
Methods: Studies were performed in paraffin tissue specimens obtained from patients undergoing surgical resection for intrahepatic CCA (n=15). Liver biopsies from implanted grafts served as controls (n=10). Immunohistochemical and immunofluorescence procedures were applied to determine the cellular expression of procoagulant factors in both tumoral and stromal compartments, using antibodies to recombinant human tissue factor (TF), factor (F) XI, FXIIIA, von Willebrand factor (vWF), fibrinogen and endothelial protein C receptor (EPCR). Martius Scarlet Blue (MSB) staining technique was used for assessing fibrin deposition and correlating local thrombosis (portal vein microthrombosis, PVT) with the above-mentioned factors.
Results: Activation of blood coagulation was variably

detected in CCA tissue, whereas it was not observed in control samples. TF was strongly expressed by tumor cholangiocytes and also by stromal cells, whereas FXI expression by tumor cells was minimal. Fibrinogen was dispersed and diffuse throughout the tumor stroma, while fibrin deposits were present in the stroma and along the tumor margins. Notably, presence of fibrin within the portal vein lumen (n=2/15), indicating the development of PVT, correlated with the strongest expression of TF by tumor cholangiocytes. FXIIIA was detected in both tumor cholangiocytes and tumor-associated macrophages (TAM), suggesting TAM as a further player of fibrin generation in the tumor matrix. Endothelial expression of EPCR was significantly weaker in tumor than in controls, supporting an additional pro-coagulant effect in CCA on the contrary to VWF, whose expression was increased in endothelial cells lining tumor-associated vasculature

Conclusions: Features of coagulation cascade activation and impaired fibrinolysis are expressed by CCA, regardless of the development of PVT. Future studies are needed to understand the role of coagulation perturbation in CCA progression, and possibly provide a rationale for testing agents that modulate the blood coagulation/fibrinolytic system in CCA.

PO013

ANTICOAGULATION REVERSAL IN A PATIENT WITH HEMOPERICARDIUM AND CARDIAC TAMPONADE TREATED WITH WARFARIN AFTER RECENT PLACEMENT OF A MECHANICAL VALVE PROSTHESIS

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Background: Life-threatening bleeding can complicate warfarin therapy. Rapid anticoagulant reversal via replacement of vitamin-K dependent factors is essential for hemostasis. We describe a patient with hemopericardium and cardiac tamponade, treated with warfarin for a mechanical valve prosthesis.

Case Report: A 33-year-old male with a recent placement of a mechanical valve prosthesis, on warfarin in the past 20 days, presented on November 3, 2023, to the ED for chest pain and dyspnea, with evidence of a large pericardial effusion. The patient underwent valve replacement surgery with a mechanical prosthesis on 27 October 2023, due to aortic bicuspid and severe aortic insufficiency. A pericardiocentesis was performed on November 3, 2023, with resolution of the pericardial effusion. Twelve days later the patient presented to the ED for syncope. The transthoracic echocardiogram evidenced hemopericardium with signs of cardiac tamponade. The laboratory evaluation showed an INR of 5.41, and severe anemia (hemoglobin 6.7 g/dl). Due to the rapid worsening of the hemodynamic conditions, the patient underwent a new pericardiocentesis, after reversal of the excessive anticoagulation with PCC 20 IU /kg body weight, and non-activated FVII concentrate 20 IU/Kg body weight, with rapid improvement of INR values (1.7). He was also given vitamin K, 10 mg intravenously, and two units of red blood cells. The pericardiocentesis was not complicated by new hemorrhages and the warfarin treatment was started soon after the procedure.

Conclusions: Acute reversal of anticoagulation may be necessary in patients undergoing surgery, or with severe bleedings. PCC, rFVIIa and non-activated FVII may be used for warfarin reversal and these agents have advantages over FFP for reducing the time required for the reversal, and the volume of transfusion. A 4F PCC reversal strategy or the combination of 3F PCC and non-activated FVII, is efficacious in INR reversal and provides lower thrombotic risk, as compared to 3F PCC+ rFVIIa, in high risk patients, as the case described.

PO014

EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS DURING PREGNANCY: A SINGLE CENTER REAL WORD EXPERIENCE

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Background and Aims: The novel direct oral anticoagulants (DOACs) represent an alternative to the traditional vitamin K antagonists (VKA) for the prevention and treatment of thrombosis. They have limited monitoring requirements, very predictable pharmacokinetic profiles and were shown to be non-inferior or superior to VKA in the prophylaxis or treatment of thromboembolic events. There are remaining limitations with DOACs: their dependence on renal and hepatic function for clearance, the interaction with other drugs and interference with functional coagulation assays. While DOACs are increasingly used for anticoagulation purposes outside pregnancy, their efficacy and safety during pregnancy is unknown due to exclusion of pregnant women in DOAC study protocols and the guidelines advise against DOAC use during pregnancy. The direct factor Xa inhibitors are partly, and dabigatran mainly, eliminated by the kidneys. Given the markedly increase of glomerular filtration rate during pregnancy and may be increased renal elimination of DOAC. Also, dabigatran inhibits clot formation by direct inhibition of factor IIa, thus decreasing the transition of fibrinogen into fibrin; in pregnancy fibrinogen levels are elevated, which is another reason that dabigatran could be insufficient in pregnant women. Additionally, DOACs have been shown to cross the placenta in perfusion models suggesting that toxic effects on the foetus. However, evidence regarding efficacy and safety during pregnancy is scarce.

Methods: We evaluate the use of DOACs during preg-

nancy in two young patients followed at our center.
The first case was a 32 year old patient with protein S deficiency and with a positive personal history of deep vein thrombosis in the left lower limb and right upper limb during her first pregnancy. She had been taking edoxaban for secondary antithrombotic prophylaxis, since June 2022, when she discovered she was pregnant and goes to our center at six at six weeks of gestation while still on oral treatment. After extensive discussion on the risks and benefits of anticoagulant therapy with direct anticoagulants during pregnancy, the patient decided to continue the pregnancy and switched to LMWH (low molecular weight heparin). In the fourth month of pregnancy she discovers serious fetal malformations (cystic hydroma and cardiac malformation) therefore therapeutic abortion is induced. The second case was a 37 year old patient with a pulmonary embolism diagnosed on November 2023, she practiced apixaban at a dosage of 5 mg x2/die until April 2024 when she discovered she was pregnant of 5 weeks. Given the exposure to the drug, interruption of pregnancy was proposed but the patient refused, so the direct oral anticoagulant was replaced with LMWH. The patient still pregnant.
Results: women of reproductive age may become pregnant during anticoagulation and, while VKA carry an embryotoxic potential, the risk of DOAC embriopathy is un known. Collections of clinical data and literature reviews are necessary to substantiate the lack of safety of new oral anticoagulants for pregnant patients. In the first case the serious fetal malformations could have been induced by the oral pharmacological therapy practiced. In the second case, frequent instrumental monitoring will allow the identification of early fetal anomalies.
Conclusions: pregnancy outcome data are inconsistent captured in pharmacovigilance databases indicating the strong need for a robust system of reporting.

PO015

EFFICACY AND SAFETY OF THERAPY WITH EDOXABAN IN THE PREVENTION OF VENOUS THROMBOEMBOLISM

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Background and Aims: Current guidelines recommend for venous thromboembolism (VTE) at least three months of anticoagulant therapy. The risk of recurrence of VTE persists after discontinuation of initial anticoagulant therapy. New evidence shows that direct-acting oral anticoagulants (DOACs) are effective for the extended treatment of VTE. The optimal duration is however controversial and complicated by the need to define the relationship between the risk of thrombotic recurrence and individual bleeding. The Purpose of the study is to define in real-life the Edoxaban's efficacy and safety for the long-term treatment of VTE.
Methods: In the Angiology Complex Operational Unit located in Padua Hospital, a sample of 82 patients affected with VTE, already treated for three months with DOACs, was monitored for a period of 6 moths of anticoagulant therapy for the prevention of relapse (Rivaroxaban 10 mg, Apixaban 2,5 mg, Edoxaban 60 mg or Edoxaban 30 mg), to reveal the possible VTE reccurence and significant clinical bleeding. Based on previous data, the significant clinical bleeding was tested with COX regression. Furthermore to evaluate the period free from haemorrhagic complications, between Edoxaban and DOACs, we used Kaplan-Meier curves.
Results: During the follow-up, 7 patients were affected with clinically relevant bleeding and 1 patient presented a thromboembolic reccurence. In our study there is no statistically significant difference in the hemorrhagic risk profile between patients treated with either Rivaroxaban 10 mg or Apixaban 2.5 mg and the group treated with Edoxaban all dosages (HR=2.5, 95%CI: 0.47-13.27, p=0.28) or Edoxaban 30 mg (HR=2.9, 95%CI: 0.46-18.3, p=0.42). Related to effectiveness, the small recurrence of thromboembolic events prevents significant statistical findings.
Conclusions: Our sample does not show a significant advantage in terms of efficacy or safety in the use of Edoxaban, at any dosage, compared to either Rivaroxaban 10 mg or Apixaban 2,5 mg. In particular, the use of Edoxaban 30 mg to prevent VTE reccurence does not appear to result in
greater safety or efficacy than other treatment groups.

PO016

THE COMPLEX MANAGEMENT OF ANTICOAGULANT THERAPY IN PATIENTS WITH MULTIMORBIDITY: AN HARD CHALLENGE FOR INTERNAL MEDICINE

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The 97th AIFA note formalizes how and when anticoagulant must be prescribed: in prophylaxis and treatment of thromboembolic diseases, heart valve diseases, mechanical valve prostheses, myocardial infarction and deep and atypical venous thrombosis. Furthermore, anticoagulant therapy is contraindicated in cases of high bleeding risk, moderate-severe hepatic insufficiency, severe renal insufficiency and marked thrombocytopenia. Patient R.B, affected by Klinefelter syndrome (KS), came to our attention, at the age of 36, because of severe anemia, hemoglobin (Hb) 4.6 mg/dl, red blood cells (RBC) $1.73x10^6/\mu L$, and platelets (PLT) 41000/µL, reporting recurrent ulcers at the lower limbs, partial amputation of the 2nd toe of the right foot and systemic lupus erythematosus (SLE). Physical examination revealed hepatomegaly and splenomegaly, with suspected ascites.

To manage the anemia, RBC transfusions and recombinant erythropoietin alpha 40000 IU were performed, with progressive improvement of related parameters. Then, patient underwent to abdominal echography, showing a spleen diameter of 22 cm, and Fibro-scan, resulting in liver cirrhosis. Computed tomography with contrast medium showed partial thrombosis of the right portal branch and concomitant diagnosis of portal hypertension. Gastroscopy (EGDS) was performed with the finding of F2 esophageal varices at the middle third of the esophagus, too. The presence of thrombosis of the right portal branch, in conjunction with the history of SLE, directed us towards the practice of acquired thrombophilia screening panel, with positivity to LAC antibodies, Anticardiolipin IgM and IgG, Anti Beta2glycoprotein IgM and IgG: these elements lead to the diagnosis of antiphospholipid syndrome (APS). This condition, associated with a high probability of contracting pulmonary embolism, led to the decision to suspend TRT and start anticoagulant therapy with low molecular weight heparin (LMWH) 4000UI every 12 hours, while constantly monitoring the platelet level. Venous Eco color-Doppler (ECD) of lower limbs, noticed femoro-popliteal-twin deep vein thrombosis (DVT). Upon admission to the facility, the patient presented mild anemia with marked thrombocytopenia, PLT: 37000/µL. The therapy carried out for DVT, according to guidelines, was an increase fondaparinux 2.5mg twice per day. After about two weeks, improvement of the hemodynamic and clinical conditions with resolution of ascites and edema, even if EGDS evidenced a worsening of the esophageal varices from F2 to F3. In the subsequent blood count tests there was a reduction in platelets from 37000 to 30000/µL, so we reduced fondaparinux 2.5 mg once a day. The increase in the platelet count occurs after about a week with values around 41000/µL. In literature, clinical cases of patients suffering from KS with DVT, and the occurrence of thrombosis have been reported both in the case of TRT and in its absence: in the second case, reduced lysis of the fibrin clot was associated with higher levels of fibrinogen and body fat related to decreased total testosterone. Consequently, fibrin clot lysis in KS is markedly reduced, potentially contributing to a greater prothrombotic state. The crux of the problem is the difficult balance, in constant and dynamic competition, between severe bleeding risk and extensive venous thromboembolism with persistent triggers in the context of multiple comorbidities which strongly influence the therapy and the patient's quality of life.

PO017

SAFETY AND EFFECTIVENESS OF FONDAPARINUX FOR LONG-TERM TREATMENT OF VENOUS THROMBOEMBOLISM: RESULTS FROM THE START REGISTRY

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Background and Aims: Fondaparinux is actually licensed for the acute treatment of venous thromboembolism (VTE), but for some favourable characteristics it is sometimes used in specific subgroups of patients also in the long-term treatment. Aim of this study was to evaluate the long-term safety and effectiveness of fondaparinux in patients with VTE.

Methods: We performed a preliminary retrospective analysis on data from the START Registry about patients receiving long-term anticoagulation with fondaparinux, direct oral anticoagulants (DOACs), vitamin k antagonists (VKAs), and low-molecular-weight heparin (LMWH). According to the type of anticoagulation, we assessed as primary safety outcomes major and non-major bleedings, and as effectiveness outcome recurrent VTE. Patients receiving fondaparinux were further matched in a 1:1 ratio by age, sex category, body mass index (BMI), and platelets with patients receiving DOACs, VKAs, and LMWH.

Results: We included 3194 patients. Among these, only 50 received Fondaparinux, while 1861 were treated with DOACs, 1808 with VKAs, and 195 with LMWH. The population characteristics are shown in Table 1. Mean age was comparable among the groups, but there were significant differences between sex category and BMI. A significantly higher proportion of patients receiving fondaparinux had a persistent risk factor and a history of previous major bleeding as well as a lower platelet count than patients receiving other anticoagulants. Regarding the safety outcomes, prevalence of major and non-major bleeding was similar between groups. Conversely, the prevalence of recurrent VTE appeared to be higher in patients receiving fondaparinux. After propensity score matching results were consistent to those of primary analysis.

Table 1.

characteristics of the population

Variables	Fondaparinux N = 50	DOACs N = 1861	VKA N = 1808	LMWH N = 195	p-values
Mean age, years (SD)	63.78 (14.40)	63.51 (17.22)	63.48 (17.69)	63.10 (17.17)	0.990
Male sex, n (%)	21 (42.0)	979 (52.6)	869 (48.1)	86 (44.1)	0.008
Mean BMI, (SD)	27.56 (5.68)	26.91 (4.44)	26.54 (5.00)	25.69 (4.75)	0.001
Family history of VTE, n (%)	9 (42.9)	217 (15.3)	256 (17.5)	17 (11.4)	0.001
Personal history of VTE, n (%)	3 (6.0)	421 (22.6)	224 (12.4)	19 (9.7)	<0.001
Risk factor of VTE, n (%)					<0.001
Unprovoked	26 (53.1)	1348 (73.4)	1244 (68.9)	63 (32.5)	
Persistent	16 (32.7)	136 (7.4)	194 (10.7)	95 (48.7)	
Transient	7 (14.3)	352 (19.2)	367 (20.3)	37 (19.0)	
Previous major bleeding, n (%)	2 (6.1)	65 (4.4)	41 (2.5)	7 (4.5)	0.019
Mean Hb, g/dl (SD)	13.24 (1.61)	18.78 (202.07)	14.64 (21.71)	12.23 (2.00)	0.797
Mean PLT, (SD)	214.16 (66.31)	241.98 (84.41)	246.70 (94.53)	236.05 (106.06)	0.025
Mean clearance creatinine, (SD)	90.98 (45.10)	89.13 (36.17)	84.64 (38.75)	87.86 (44.73)	0.004
Mean AST, UI/L (SD)	26.77 (14.94)	23.71 (21.69)	27.10 (35.42)	28.40 (29.67)	0.013
Mean ALT, UI/L (SD)	33.97 (35.87)	25.62 (23.27)	28.43 (28.94)	27.89 (29.01)	0.017
Outcomes					
Major bleeding, n (%)	1 (2.0)	24 (1.3)	33 (1.8)	2 (1.0)	0.001
Non-major bleeding, n (%)	1 (2.0)	29 (1.6)	70 (3.9)	3 (1.5)	0.001
Recurrent VTE, n (%)	3 (6.0)	46 (2.5)	12 (0.7)	4 (2.1)	<0.001

Conclusions: In this preliminary analysis on patients receiving fondaparinux for long-term treatment of VTE, the prevalence of bleedings was similar and that of recurrent VTE slightly higher than other licenced anticoagulants. Caution is needed for the interpretation of these results, which are limited by the small sample size of our cohort. Larger cohorts are needed to confirm these findings.

PO018

VARIATION OF EGFR IN PATIENT IN DOACS THERAPY

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Background and Aims: The introduction of direct oral anticoagulant drugs (DOACs) into clinical practice has represented a revolution in the prevention and treatment of thrombotic events in different clinical settings. Their use is now well established in the prevention of systemic thromboembolism in patients with non-valvular atrial fibrillation (AF) and in the prophylaxis and treatment of venous thromboembolism (VTE). Their application is also expanding in other clinical settings. The factors that have led to such a large diffusion of DOACs lie essentially in their pharmacological characteristics. The more predictable dose-response relationship, the lower interaction with other drugs and with food, and the overcoming of the need to monitor anticoagulant activity represent undoubted advantages over vitamin K antagonists (VKAs). However, the use of DOACs should be evaluated during therapy based on several data, including liver and kidney function. This study focused on the change in renal function during therapy and as age increased.
Methods: We conducted a retrospective observational study on patients enrolled in the Hemostasis Center of the AORN S. Moscati (AV) and receiving therapy with DOACs (dabigatran, rivaroxaban, apixaban and edoxaban). The study court consists of 105 patients aged 21-90 years. The study cohort was divided into four groups: patients aged <40 years; patients aged 41-60; patients aged 61-75; patients aged >76 years. Patients were periodically evaluated for glomerular filtration rate (eGFR) according to the following schedule: - First assessment after six months of treatment. - Second assessment after 12 months of treatment. - Third assessment after 18 months of treatment. - Fourth assessment after 24 months of treatment.
Results: From November 2013 to March 2022, 105 patients (43 males) with DOACs therapy were included in the study. At entry, the mean patient age was 65 +/- 4 years. 38% in edoxaban (4% in low dose), 17% in apixaban (4% in low dose), 2% in dabigatran (150mg), 43% in rivaroxaban (25% in low dose and 8% in medium dose). The eGFR was calculated using the Cockcroft-Gault formula. The reduction in eGFR capacity is indirectly proportional to advancing age. The group with the greatest change in eGFR was patients aged >76 years. Conversely, the group with a miron variation in eGFR was the one aged 41-60 years (Figure 1).
Conclusions: DOACs, due to their pharmacological characteristics and safety profile, have represented an important step forward in anticoagulant therapy. The potential loss of some of their most advantageous properties, such as the predictability of the dose-response relationship, implies that their use must be carefully evaluated especially in patients with an advanced age as these are more critical: they represented the group with the greatest variation in eGFR.

Figure 1.

PO019

EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS FOR TREATMENT OF CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM IN A LONG TERM FOLLOW-UP. A REAL-LIFE ITALIAN REGISTRY (MAC PROJECT)

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Background: Extended-phase anticoagulation with direct oral Xa inhibitors (DOACs) is suggested in patients with cancer-associated venous thromboembolism (CAT).
Aims: We report on patients enrolled in the real-life italian MAC registry, given DOACs as extended-phase anticoagulation after CAT.

Methods: The MAC Project is a prospective cohort, multi-center, observational, no-profit study. The project aims to collect real-life clinical information in unselected patients investigated in Italian hospital-based clinical centres and given DOACs for venous thromboembolism over a 5-year follow-up period. There are no exclusion criteria, except for life expectancy <6 months and refusal to sign the informed consent form or to attend the planned follow-up visit. All patients are followed-up prospectively with clinical controls scheduled at 3, 6, and 12 months after the index event, and then annually for up to 5 years. All DOACs are prescribed according to current standards of care and regulations and not provided by any sponsor. The primary efficacy and safety outcomes are symptomatic recurrent VTE and major bleeding.
Results: From September 2018 a total of 1528 consecutive patients have been included. Of them 264 (17.2%) had cancer and 1264 (82.8%) had not. Recurrent VTE occurred in 3.8% (IR 3.8 per 100 person-years; 95%CI 1.7-7.0) and in 6.3% (IR 3.5 per 100 person-years; 95%CI 2.8-4.4) of patients with and without CAT (p=0.183). Major bleeding occurred in 2.3% (IR 2.3 per 100 person-years; 95%CI 0.8-4.9) and in 1.5% (IR 0.8 per 100 person-years; 95%CI 0.5-1.3), respectively (p=0.898). The relative figures for fatal bleeding and all-cause death were 0.4% *versus* 0.1%, and 0.4% *versus* 0.1% (p=0.3). The mean follow-up was 20.3 (±19.4 SD) and 24.3 (±20.2 SD) months, respectively
Conclusions: DOACs appear to be as effective as safe for extended-phase anticoagulation in patients with CAT. Observation is still ongoing in a longer follow-up period

PO020

EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS FOR TREATMENT OF VENOUS THROMBOEMBOLISM IN A LONG-TERM FOLLOW-UP. A REAL-LIFE ITALIAN REGISTRY (MAC PROJECT)

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Background: Real-life studies on direct oral anticoagulants (DOACs) for treatment of venous thromboembolism (VTE) aim to confirm the results of the registrative trials. Because of delayed registration of DOACs in Italy, scarce real-life data is currently available in the Italian population
Aims: To prospectively collect reliable real-life clinical information in unselected VTE patients treated with DOACs during a long term follow-up period
Methods: The MAC Project is a prospective cohort, multi-center, observational, no-profit study. The project aims to collect real-life clinical information in unselected patients investigated in Italian hospital-based clinical centres and given DOACs for VTE over a 5-year follow-up period. There are no exclusion criteria, except for life expectancy <6 months and refusal to sign the informed consent form or to attend the planned follow-up visit. All patients are followed-up prospectively with clinical controls scheduled at 3, 6, and 12 months after the index event, and then annually for up to 5 years. All DOACs are prescribed according to current standards of care and regulations and not provided by any sponsor. The primary efficacy and safety outcomes are symptomatic recurrent VTE and major bleeding.
Results: From September 2018 a total of 1528 consecutive patients have been included. Of them, 843 (55.1%) had unprovoked VTE; 1257 (82.2%) were symptomatic. During a mean 23.7-month follow-up (±20.1 standard deviation) recurrent VTE occurred in 90 patients (5.9%) (IR 4.7 per 100 person-years; 95%CI 3.7-5.8). Overall, bleeding events occurred in 68 (4.4%) patients, of which 2 fatal bleeding (0.1%) and 25 major bleeding (1.6%). Two patients died for other than VTE-related causes.
Conclusions: DOACs showed to be as safe as effective for the long-term VTE treatment in italian patients. Our results match previously published data of other international registries. The observation is still ongoing with the aim of collecting data in a longer follow-up

PO021

EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS FOR TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH RENAL INSUFFICIENCY IN A LONG-TERM FOLLOW-UP. A REAL-LIFE ITALIAN REGISTRY (MAC PROJECT)

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Background: Anticoagulation with direct oral Xa inhibitors (DOACs) in patients with venous thromboem-

bolism (VTE) and renal insufficiency still is matter of debate and long-term data is lacking.
Aims: We report on patients enrolled in the real-life italian MAC registry, given DOACs as extended-phase anticoagulation in patients with VTE and different degrees of renal insufficency.
Methods: The MAC Project is a prospective cohort, multi-center, observational, no-profit study. The project aims to collect real-life clinical information in unselected patients investigated in Italian hospital-based clinical centres and given DOACs for venous thromboembolism over a 5-year follow-up period. There are no exclusion criteria, except for life expectancy <6 months and refusal to sign the informed consent form or to attend the planned follow-up visit. All patients are followed-up prospectively with clinical controls scheduled at 3, 6, and 12 months after the index event, and then annually for up to 5 years. All DOACs are prescribed according to current standards of care and regulations and not provided by any sponsor. The primary efficacy and safety outcomes are symptomatic recurrent VTE and major bleeding.
Results: From September 2018 a total of 1528 consecutive patients have been included. Of them, 989 had a valid creatinine clearance (CrCl) value. Overall, 754 (76.2%) had a CrCl 50-79 ml/min, 201 (20.3%) a CrCl 30-50 ml/min, and 34 (3.5%) a CrCl 15-29 ml/min. No significant statistical difference was found for VTE recurrrence among the three groups (8.0%, 8.0%, and 5.9%, respectively; p=0.907). A significant statistical difference was found for total bleeding among the three groups (5.3%, 10.4%, and 14.7%, respectively; p=0.006)
Conclusions: In patients with different degrees of renal insufficiency, the use of DOACs for VTE treatment has been shown to be equivalent in preventing VTE recurrence, but showed an increased risk of bleeding as renal function worsened

PO022

REDUCED-DOSE DOAC AS SECONDARY PROPHYLAXIS IN A COHORT OF PATIENTS WITH SEVERE THROMBOPHILIA

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Background and Aims: Thrombophilia is a condition associated with an increased risk of thromboembolism (TE). It may be caused by inherited or acquired conditions. For patients (pts) with thrombophilia, who had an episode of TE, guidelines suggest long-term anticoagulation for secondary prophylaxis. Retrospective and prospective studies and clinical trials showing that full-dose DOAC appears to be effective and safe in the treatment of TE in this group of pts, even in long term utilization. Fewer data, however, are available for secondary prophylaxis using reduced-dose DOAC (rdDOAC).
Methods: Data on a subgroup of pts with a severe thrombophilia who had a TE history, treated in secondary prophylaxis with rdDOAC between March 2017 and May 2024, was retrospectively collected and analyzed. Our cohort include pts with antiphospholipid syndrome (APS) (n=7), homozygous factor V Leiden (fVL) (n=5), antithrombin (AT) deficiency (n=7), protein C (pC) deficiency (n=3), protein S (pS) deficiency (n=5), combined thrombophilias defined as ≥2 between AT or pC or pS deficiency, homozygous or heterozygous mutations of fVL or prothrombin (fII), APS (n=24).
Results: A total of 51 thrombophilic pts were treated with rdDOAC in secondary prophylaxis; 30 received rivaroxaban 10 mg/day (R group; Rg) and 21 received apixaban 2.5 mg x 2/day (A group; Ag). Median follow-up in rdDOAC was 27 months in Ag and 23 months in Rg. Characteristics of population are summarized in Table 1. During rdDOAC prophylaxis 3 pts (5,9%) had a TE event, all venous type; 2 pts (9,5%) in the Ag, one of which was a superficial vein thrombosis (SVT) and 1 pts (3,3%) in the Rg; they had 3 different thrombophilias: homozygous fVL, pS deficiency and heterozygous fII plus pS deficiency. 3/3 had an additional transient thrombotic risk factor: hospitalization for progressing cancer disease in therapy with bevacizumab, erysipelas in pts with BMI >30 and recent venous cannulation. The median duration of prophylaxis at time of event was 24 months (range 12-33). At 12 months, 1 pts (4.8%) in Ag and 0 pts in Rg experienced a TE event. During rdDOAC 3 pts (5,9%) had a hemorrhagic event; 1 pts (3,3%) in the Rg and 2 pts (9,5%) in the Ag, one of which was a major bleeding. The last one was a hemorrhoidal bleeding in pts with additional hemorrhagic risk factors (advanced age and hypertension). The other hemorrhagic events were hematuria and a self-limiting bleeding in post-thrombotic ulcers. The median duration of prophylaxis at time of event was 25 months (range 10-28).

Table 1.

	Apixaban N=21	Rivaroxaban N=30	All N=51	p. overall
Median follow-up in rdDOAC (months) [IQR]	27 [19;64]	23 [15;34]	24 [16;34]	0.174
Male	13 (61.9%)	16 (53.3%)	29 (56.9%)	0.748
Female	8 (38.1%)	14 (46.7%)	22 (43.1%)	
Median age at first TE (years) [IQR]	60 [40;70]	40 [30;60]	45 [31;65]	0.036
Mean number of previously TE	1 [0;1]	1 [0;1]	1 [0;1]	0.469
TE events in rdDOAC	2 (9.5%)	1 (3.3%)	3 (5.9%)	0.561
BMI > 30	2 (9.5%)	7 (23.3%)	9 (17.6%)	0.277
Active cancer	4 (19.0%)	3 (10.0%)	7 (13.7%)	0.606
All bleeding during rdDOAC	2 (9.5%)	1 (3.3%)	3 (5.9%)	0.561
Status:				
Alive	16 (76.2%)	27 (90.0%)	43 (84.3%)	
Death	2 (9.5%)	1 (3.3%)	3 (5.9%)	
Lost at follow-up	3 (14.3%)	2 (6.7%)	5 (9.8%)	

Conclusions: In our cohort of pts with high thrombophilic risk the use of rdDOAC in secondary prophylaxis has been shown to be safe and effective, regardless of the type of DOAC employed. We observed a comparable recurrence rate of TE and lower risk of bleeding than in studies of full-dose DOACs which include pts with known thrombophilia. Moreover, all TE recurrences were not idiopathic but occurred in pts with additional transient prothrombotic risk factors. The limitation of these data is the retrospective nature and the low number of patients included in the statistical analysis.

PO023

ORAL ANTICOAGULANTS AND BLEEDING IN REPRODUCTIVE AGE WOMEN: FIBROIDS MATTER

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Background: Up to 70% of anticoagulated menstruating women experience Heavy Menstrual Bleeding (HMB) , which commonly results in iron deficiency with/without anemia. Limited studies indicate that Direct Oral Anticoagulants (DOACs) may have a more favorable bleeding profile compared to Vitamin K Antagonists (VKAs).
Methods: We retrospectively identified medical records of women between 18–50 years observed at our anticoagulation clinic for venous thromboemboembolism (VTE) from September 2016 to October 2023. Type of Oral Anticoagulants (OAC) prescribed, age at OAC initiation, and general demographics were recorded. A case record was excluded if surgical menopause was documented prior to OAC initiation, or if OAC use was within 6 months of a pregnancy or within 3 months of lactation. Women not receiving follow up care within our healthcare system were excluded. Complete blood count and the Pictorial Blood Assessment Chart (PBAC) at enrollment and during therapy were used to assess menstrual blood loss. We used descriptive statistics and multiple ANOVA (MANOVA) to evaluate associations between OAC type, DOAC class, age, PBAC, diagnosis of fibroids and difference in hemoglobin levels during *vs* before OAC.
Results: Overall, 110 women met inclusion criteria (Table 1), all took therapeutic doses. No difference in prescription of type of OAC was observed by age or type of VTE, with the exception of women with CVT who were significantly more prescribed with VKA than DOAC (25.8% *vs* 8.3%, p: 0.02). We calculated delta hemoglobin (Hb), *i.e.* difference between Hb during minus Hb before therapy –that was not significantly higher in those taking VKAs *vs* DOAC. However, those taking apixaban showed a significantly difference in delta Hb also after correction for potential confounders (age, fibroids, comorbidities, duration of anticoagulation, iron therapy p: 0.004). Delta Hb was significantly different among those with fibroids compared to those without (median -0.3,IQR -3, 2.9 *vs* -0.5, IQR -1.2,-0.3 p: 0.012) Noteworthy, among women with fibroids, those taking apixaban showed a safer delta Hb profile compared to those taking other OAC (p: 0.047).
Conclusions: The choice of OAC in fertile women should take into account sex-specific characteristics. In our cohort apixaban showed the safest profile even for those with fibroids.

Table 1.

	Anticoagulant therapy[1]:			
	Overall, N = 110[1]	DOAC, N = 48[1]	VKA, N = 62[1]	p value[2]
Age at diagnosis, years	36(27,44)	42 (35, 45)	32 (24, 39)	0.00
BMI, Kg/m2	26.1 (22.8, 29.7)	26.6 (23.9, 29.5)	25.7 (21.8, 30.3)	0.48
smokers	17/109(16%)	7/48 (15%)	10/61 (16%)	0.80
Oral Contraceptives	42/ 110 (38%)	16/48(33%)	26 / 62 (42%)	0.36
hypertension	11 / 110 (10%)	7 / 48 (15%)	4 / 62 (6.5%)	0.16
Diabetes	5/ 110 (4.5%)	2 / 48 (4.2%)	3 / 62 (4.8%)	0.87
Autoimmune disease	27 / 110 (25%)	11/48 (23%)	16 / 62 (26%)	0.73
Cancer	6 / 110 (5.5%)	2 / 48 (4.2%)	4 / 62 (6.5%)	0.60
Uterine fibroids	17 / 31 (55%)	10/13(77%)	7/ 18 (39%)	0.04
Other comorbidities	8 / 110 (7.3%)	6/48(13%)	2/ 62 (3.2%)	0.06
Varicose veins	22/ 109 (20%)	14 / 47 (30%)	8 / 62 (13%)	0.03
PBAC				
Basal	120 (65, 287)	134 (63, 282)	101 (67, 300)	0.82
during treatment	301 (94, 443)	301 (89, 427)	301 (100, 464)	0.61
Δ	36 (0, 190)	38 (0, 190)	30 (0,181)	0.75

[1]Median (25th-75th percentile) or Frequency (%)
[2]Two Sample t-test; Wilcoxon rank sum test; Pearson's Chi-squared test
PBAC: Pictorial Blood Assessment Chart

PO024

MILD-MODERATE FACTOR XI DEFICIENCY IN PREGNANCY: BIRTH MANAGEMENT

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Background and Aims: Unlike many other clotting factors, Factor XI (FXI) does not increase during pregnancy. In patients with FXI deficiency bleeding tendency is unpredictable and unrelated to plasma factor levels making management during pregnancy and childbirth particularly challenging. Therefore, even women with non-severe deficiency (heterozygotes with FXI levels 20-70% of normal) need a careful plan for birth management. We assessed the risk of postpartum hemorrhage (PPH: blood loss ≧ 1000 ml or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours of childbirth - ACOG Criteria 2017) in women with mild-moderate FXI deficiency undergoing vaginal delivery or cesarean section.
Methods: We evaluated pregnant women with FXI

deficiency referred to our center for «prolonged aPTT» in tests scheduled for epidural/spinal anesthesia. We collected information about bleeding history according to the ISTH Bleeding Assessment Tool (BAT) and obstetric risk factors (ISS Italian Guidelines 2016). Afterwards, we collected information about the delivery with particular interest for the type of delivery (vaginal or cesarean section), the use of neuraxial anesthesia, the incidence of PPH and the therapy for bleeding control/bleeding prophylaxis.

Results: From July 2021 to April 2024 we consecutively identified 40 women with mild-moderate FXI deficiency (mean plasma levels 54%). The incidence of PPH was 12.5%: 3 vaginal deliveries (10.3%) and 2 cesarean sections (18.18%) were complicated by PPH. The high incidence of PPH in vaginal deliveries, despite a lower obstetric risk, can be explained by a higher number of women with positive BAT-score in this group (37.9% *vs* 27%) and probably reflects a lower use of antifibrinolytics and uterotonics in vaginal delivery when compared to cesarean section (20.7% *vs* 45%). Plasma prophylaxis was used only in a patient undergoing cesarean section with FXI level of 40% and with a positive BAT-score. Finally neuraxial anesthesia was performed in 13 patients (mostly in the cesarean section group), without bleeding complications. The study results are summarized in the Table 1.

Table 1.

results

	VAGINAL DELIVERIES	CESAREAN SECTIONS
Number of pregnancy	29/40	11/40
Age	31.48 (23-44 years)	35.45 (28-44 years)
aPTT	1.41	1.47
FXI levels	54.7%	53.54%
Positive BAT-score	11/29 (37.9%)	3/11 (27%)
PPH	3/29 (10.3%)	2/11 (18.18%)
≥ 1 obstetric risk factors for PPH	10/29 (34.5%)	6/11 (54.5%)
Neuraxial Anesthesia	4/29 (13.8%) (2/5 with Antifibrinolytics prophylaxis)	9/11 (81%) (3/9 with Antifibrinolytics prophylaxis)
Antifibrinolytics use	6/29 (20.7%)	5/11 (45%)
Plasma	3/29 (10.3%) in PPH	2/11 (18.18%) 1 in PPH e 1 in prophylaxis

Conclusions: Even patients with mild-moderate FXI deficiency have a greater hemorrhagic risk than the general population, regardless of the type of delivery (18.18% *vs* 5-10% for cesarean section and 10.3% *vs* 3% for vaginal birth). Previous bleeding history was confirmed as the greatest predictor of PPH, regardless of the type of delivery. Therefore even in vaginal deliveries the use of antifibrinolytics should be implemented. The use of plasma prophylaxis does not appear to be strictly necessary: the decision on its administration should not be dictated by FXI levels but should assess bleeding history and additional obstetric risk factors. Based on these observations, we believe that women with FXI deficiency should be evaluated with a multidisciplinary approach (obstetrician, obstetric anesthesiologis and hematologist).

PO025

AN EPISODE OF PE IN A FEMALE WITH MILD HEMOPHILIA B: A CASE REPORT

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Background: Haemophilia is a rare genetic disorder, that results from various degrees of deficiency of coagulation factor VIII (haemophilia A), or factor IX (haemophilia B), with an X-linked transmission. The patients affected are in the majority of cases males (who inherit the affected X-chromosome from the maternal side), with rare cases of females with haemophilia (FVIII or FIX <40 IU/dL), situations in which both X-chromosomes are affected, or one is affected, and the other one is inactive (known as carrier). The hypocoagulable state due to the deficiency of clotting factors, manifests as an excessive, recurrent tendency to bleeding, which positively correlates with plasmatic levels. There is a debate about considering patients with haemophilia at low thromboembolic risk. The great heterogeneity of this particular population and the lack of clinical studies makes it difficult to identify patients at risk of developing venous thrombohemolism. This clinical case shows that a female with mild hemophilia B is not free from thrombotic events.

Case Report: A 36-year-old patient has been diagnosed with mild hemophilia B since 2022. Genetic investigation was carried out by gene amplification (PCR) and direct sequencing according to standard methods for the study of gene 9 to search for the causative mutation of haemophilia B in the patient's family, c-55G>T (g.4975 g>t) in the 5'UTR region of the F9 gene with confirmation of the condition of heter5ozygosis for the mutation. Coagulation tests showed an APTT Ratio of 1,28 with a factor IX level of 31% and an International Normalized Ratio (INR) of 1.38, there was a concomitant deficiency of factor VII which level was 38%. The patient reports episodes of frequent epistaxis which require nasal packing with tranexamic acid and heavy menstrual cycles. two full-term pregnancies with no reported bleeding episodes. In 2023 he was diagnosed with a pulmonary embolism in another center. The patient leads a fairly healthy lifestyle but has a fairly sedentary job and venous insufficiency of the lower limbs as risk factors of thromboembolism. TC shows:" uneven opacification of some subsegmental arterial branches is appreciated for the basal-anterior and basal-lateral segments of the LIS". Thrombophilic study was normal. She began treatment with low molecular weight heparin. Heparin was administered for about a month at an intermediate dosage and then suspended in another centre. The patient comes to our observation after discontinuation of heparin (Figure 1).

Conclusions: Hemophilia patients (HP) were considered as naturally-anticoagulated and therefore protected from thrombosis. They are, therefore, liable to be affected by the circumstantial risk factors of venous

thromboembolism (VTE) that are common in the general population. We need more scientific trials to stratify patients risk with haemophilia and with other clotting factor deficiencies.

PT INR	1,38
APTT Ratio	1,23
Fib	246 mg/dl
FIX	31%
FVII	38%
Mut	Absent
Mut G20210A	Absent
AT III	105 %
PC	99%
PS	85%
LAC	0,99 R/R
ACA IgM	14,7 U/ml
ACA IgG	1,6 U/ml
Ab Antiβ² GP1 IgM	2,3 U/ml
Ab Antiβ² GP1 IgG	1,5 U/ml

Figure 1.

PO026

PATH: PREGNANCY-ASSOCIATED THROMBOSIS, HEMORRHAGE, AND ANEMIA

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Background: Maternal mortality remains a significant concern worldwide, with high rates recorded both in developed and developing countries. Post Partum Hemorrhage (PPH) and venous thromboembolism (VTE) are the leading causes of mortality and morbidity during pregnancy and the postpartum period. Anemia during pregnancy impacts on maternal and fetal wellbeing, with adverse outcomes such as PPH and VTE. Recent studies have highlighted the importance of early identification and treatment of anemia during pregnancy to mitigate its adverse effects. However, barriers to diagnosis and treatment persist, ranging from inadequate guidelines to cultural beliefs and resource constraints.
Objectives To define a plan for applying/ improving risk assessment stratifying by low- high-income countries (rural *vs.* urban/suburban) and according to management at Academic *vs.* Community Medical Centers.
Methods: A prospective question-based survey to be adminstered to medical and other health care professionals (HCP) involved in the diagnosis and management of pregnancy. Approximately 30-50 centers worldwide will be targeted for participation, representing different health care settings and different geographic regions globally. Demographic data will be collected about the participating centers and HCP. We will collect data on pregnancies, local routine practices on anemia detection, estimates of the prevalence of peripartum bleeding and thrombosis, as well as barriers and challenges to assessing risks or identification or treatment of anemia during pregnancy. ISTH REDCap will be used for designing the questionnaire. The questionnaire link will be shared in ISTH My Community to enhance participation. Participation can also be invited via personal communications, emails various relevant societies, and international meetings. Each site will be responsible for obtaining the necessary ethics approval.
Results: The project seeks to reduce maternal morbidity and mortality associated with anemia-related complications during pregnancy and the postpartum period.
Conclusions: Given the critical role of anemia in exacerbating risks associated with PPH and VTE during pregnancy, this international project aims to increase awareness and improve management strategies for anemia.

PO027

EVOLOCUMAB AND ALIROCUMAB: LDL-C TARGET PREDICTORS

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Background: There is a growing gap between the ideal guidelines LDL-C targets and the LDL-C levels achieved in clinical practice. Indeed, real world data show that about 80% of (very) high risk patients disregarded guideline recommendations. Therefore, our aim was to provide data of PCSK9i use in clinical practice investigating the adherence to guideline recommendations, with a focus on the role of background oral lower lipid therapy in the probability of target attainment.
Methods: Between April 2018 and December 2023, patients evaluated at our center and started PCSK9-i therapy were included in a prospective registry. The lipid profile was assessed before starting PCSK9i therapy, and during follow-ups that were performed every six months, with a median follow-up of 24 (6-48) months. Results are presented for the total population and stratified by patient subgroups: high risk patients with asymptomatic heterozygous familial hypercholesterolemia (LDL-C target <70 mg/dl) and very hight risk patients with known atherosclerotic cardiovascular disease (LDL-C target <55 mg/dl).
Results: Our cohort consisted of 271 patients: 100 (36,9%) women, mean age of 65,1±11,1 years, 60 (22,1%) at high risk and 211 (77.9%) ad very high risk. Nearly 60% of patients demonstrated full adherence to

ESC guideline recommendations after one year of PCSK9mAb treatment, defined as achieving at least a 50% reduction in LDL-C levels along with reaching LDL-C target levels based on the cardiovascular risk classification (≤55 and ≤70 mg/dl respectively).
A background oral LLT involving a high-dose statin emerged as the primary predictor of LDL-C target attainment. Thus, statins can't be regarded as an outdated therapy but as the ground on which built the treatment of cardiovascular prevention (primary and secondary). HeFH and statin intolerance were associated with a significant lower probability of achieving LDL-C target levels. (Un)expectedly female gender also emerged as a negative predictive factor for a favorable treatment response.
Conclusions: In conclusion, our analysis confirms that PCSK9mAb are safe and effective drugs, allowing most patients of our cohort to reach LDL-C target through a 55-60% reduction. The concurrent use of oral lipid-lowering therapy, particularly high-intensity statins, emerged as a crucial factor in our cohort, significantly influencing therapeutic outcomes. Thus, our findings underscore the importance of combination therapy in effectively managing patients at (very) high cardiovascular risk and the necessity of its persistence over time. Additionally, familial hypercholesterolemia and female gender were identified as predictors of therapeutic failure. Hence, it is crucial to address disparities in cardiovascular disease prevention between genders and to enhance strategies for managing elevated LDL-C in HeFH patients. These steps are essential for ensuring equitable access to effective treatment and improving outcomes for all patients at risk of cardiovascular disease.

PO028

RISK FACTORS OF VENOUS THROMBOEMBOLISM ASSOCIATED WITH HORMONAL CONTRACEPTION IN CARRIERS OF ANTITHROMBIN, PROTEIN C AND PROTEIN S DEFICIENCY

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Background and Aims: Thrombosis in women undergoing hormonal contraception (HC) is a rare but serious complication in the general population. Only a few studies to date have addressed the thrombotic risk associated with HC in women with a congenital deficiency of natural anticoagulants, such as protein C (PC), protein S (PS) and antithrombin (AT). We conducted a retrospective case-control study aiming to assess the venous thromboembolic (VTE) risk in carriers of AT, PC and PS deficiencies undergoing either combination oral contraceptives (COCs) or progestin-only pills (POPs).
Methods: A retrospective chart review of female carriers of AT, PC and PS deficiencies diagnosed at the department of internal medicine of Padova University Hospital, between January 2000 and December 2023, was performed. Thrombophilic women with VTE events acted as cases and those without VTE acted as controls. Demographic characteristics, type of VTE and acquired thrombotic risk factors, especially type and duration of HC, were recorded. The relative risks (RR) of developing VTE and their 95% confidence intervals (CI) were calculated for COCs and POPs.
Results: Sixty-seven cases (median age 40 yrs, range 31-48) and 140 controls (median age 32 yrs, range 20-47) were enrolled: 17 (age cases and 29 controls for AT deficiency; PC deficiency 25 cases and 49 controls for PC deficiency; 25 cases and 62 controls for PS deficiency. The relative risk (RR) of developing VTE was significantly higher in women treated with *vs.* without COCs in each of the three thrombophilia groups considered (Table 1). No significant differences were found in women treated with *vs.* without POPs (Table 1).
Conclusions: We observed a significantly increased risk of developing VTE in female carriers of congenital deficiency of natural anticoagulants undergoing COCs. No significant increase of VTE risk was observed in carriers undergoing POPs therapy. Our findings indicate that POPs may be a safe HC, not only in non-thrombophilic women as previously described in the literature, but also in women with severe thrombophilias. Larger prospective studies are needed to confirm our findings.

Table 1.

Relative risk for VTE according to the type of HC

	RR [95% CI]	P value
AT deficiency		
COCs	4.89 [1.00-23.93]	0.04
POPs	1.22 [0.19-7.90]	0.83
PC deficiency		
COCs	3.36 [1.11-10.17]	0.03
POPs	0.76 [0.18-3.31]	0.72
PS deficiency		
COCs	3.02 [1.09-8.39]	0.03
POPs	0.61 [0.12-3.24]	0.56

AT, antithrombin; PC, protein C; PS, protein S; RR, relative risk; COCs, combination oral contraceptives; POPs, progestin-only pills.

PO029

ABNORMAL UTERINE BLEEDING AND HEMOCOAGULATIVE DISORDERS IN ADOLESCENCE: A CROSS-SECTIONAL STUDY

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Background and Aims: Abnormal uterine bleeding (AUB) affects 3-20% of women of childbearing age and

most commonly adolescents. AUB includes irregularities in the menstrual cycle about the frequency, duration, regularity and volume of flow. The most frequent pattern in adolescents is «heavy menstrual bleeding» (HMB), defined by menstruation lasting more than 7 days or blood loss exceeding 80 ml/cycle. Dysfunctional causes (85-90%) depend on immaturity of the hypothalamic-pituitary-ovarian axis resulting in anovulatory cycles and dysfunctional uterine bleeding (DUB). Coagulopathies are the second leading cause of HMB in adolescents and, among them, von Willebrand disease is the most common. The aim of our study was to investigate the prevalence of hemocoagulative disorders in adolescents with abnormal uterine bleeding and identify predictive factors of bleeding disorders.

Methods: A single-center cross-sectional study was conducted on 130 patients, aged 10 to 17 years, with abnormal uterine bleeding (AUB), referred to the Endocrinology Center and Hemostasis and Thrombosis Center of Bambino Gesù Children's Hospital, in the period between January 2012 and December 2022. Primary outcome was to investigate the prevalence of hemocoagulative disorders in adolescents with abnormal uterine bleeding, describing the most frequent types of bleeding disorders at this age. Secondary outcome was to identify any clinical-biochemical factors predictive of hemocoagulative disorder in adolescents.

Results: We identified 20 (15.4%) adolescents with hemocoagulative disorders (group 1), including 10 with vWF deficiency (70% vWD type 1, 30% vWD type 2), 2 with thrombocytopenia (10%), 8 with coagulation factor deficiency (40%); in the remaining 110 adolescents (84.6%, group 2), no hemocoagulative disorders had been found. At diagnosis, mean ferritin levels were significantly lower in group 1 (11.82 ng/mL) than in group 2 (21.67 ng/mL; P=0.016). Mean levels of dehydroepiandrosterone sulfate (DHEAS) were significantly higher in group 2 (1561,3 *vs* 1059; P= 0,04). Furthermore, both personal history of bleeding beyond menometrorrhagia (*e.g.*, epistaxis and gingivorrhagia) and family history of hemorrhagic diathesis were significantly more common in coagulopathic adolescents. No statistically significant difference between the two groups was observed concerning the age of menarche, mean hemoglobin level at diagnosis, severe anemia (Hb <8 g/dL), platelet count, prothrombin time, activated partial thromboplastin time and fibrinogen, family history for menstrual cycle disorders, hospitalization and blood transfusion.

Conclusions: AUB within the first 2 years after menarche could be the first sign of an underlying hemocoagulative disorder. According to our data, hypoferritinemia at onset could be a predictive biochemical parameter of coagulopathy, an indicator of chronicity of the disease; moreover, higher levels of DHEAS in no-coagulopathic adolescents confirm that hormonal imbalance implies the dysfunctional nature of AUB. Early diagnosis is necessary to identify a bleeding disorder in order to prevent possible complications, such as bleeding secondary to trauma, childbirth and surgery, to ensure genetic counseling for offspring and appropriate therapeutic management.

PO030

GENDER CARDIOVASCULAR RISK DIFFERENCES IN PATIENTS ON SENDOCANDARY PREVENTION EVALUATED WITH PLATELET FUNCTION TESTING

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Background and Aims: Cardiovascular diseases (CVDs) represent a significant global health challenge, with ischemic heart disease being the leading cause of death worldwide. Although women usually have a lower incidence of CVDs than men, clinical evidence demonstrated that they have a higher rate of mortality and poorer prognosis following acute CV events leading to more than one third of all female deaths. Furthermore, clinical studies found important gender differences on the efficacy of antiplatelet agents to prevent CV events. This study aims to investigate gender-specific variations in platelet reactivity and response to antiplatelet therapies among individuals with different cardiovascular risk profiles.

Methods: From a single center database analysis involving 11,913 individuals (01/01/2004-31/12/2022) subjects were categorized into five groups divided based on sex after application of exclusion criteria: healthy volunteers (HV; F 273, M 155), controls (CTR; F 725, M 330) with cardiovascular risk factors, patients on aspirin 75-150 mg (ASA; F 2058, M 1231), patients on clopidogrel 75 mg (CLOP; F 272, M158), and patients on dual antiplatelet therapy with aspirin 75-150 mg plus clopidogrel 75 mg (DAPT; F 166, M 319). Platelet function testing (PFT) was conducted using light transmission aggregometry (LTA) using ADP 2 µM, collagen (COL) 2 µg/ml, epinephrine (EPI) 10 µM, arachidonic acid (AA) 0.5 µM in HV, CTR, CLOP and AA 0.75 µM in ASA e DAPT. Statistical analysis was performed to compare PA at 4 minutes between genders within each group. Median and interquartile (IQR) are reported.

Results: There were no major clinical differences in risk factors and therapies between genders. Significant higher responses to ADP [85 (45-93) *vs* 70 (0-91); p=0.004] were observed in females of HV; in CTR population significant differences between females and males were observed in response to ADP [90 (70-94) *vs* 86 (36-93); p<0.001] and COL [92 (89-95) *vs* 93 (90-95); p=0.007] but not EPI and AA. In ASA group, females exhibited higher PA in response to ADP [49 (20-69) *vs* 40 (0-61); p<0.001] and COL [42 (24-68) *vs* 35 (20-57); p<0.001], but not to EPI and AA. No significant differences were found in CLOP or DAPT therapy in all agonists used.

Conclusions: Gender differences have been found in ASA group potentially indicating both a greater risk of

cardiovascular events and higher platelet reactivity. Similarly to the PA differences found in CTR population, in the ASA population females response is higher to both ADP and COL compared to males, strongly suggesting that women are less sensitive to aspirin treatment as for the presence of an hyper-reactive platelet phenotype. These findings are consistent with clinical evidence of reduced efficacy of aspirin on myocardial infarction and major coronary events in women compared to men and may clarify some controversial data. PA in patients on clopidogrel did not show significant differences. These results clarify the recent clinical controversies if the response of CLOP patients varies based on gender in males and females. Despite increased awareness, gender disparities persist in the understanding and management of CVD. Understanding these differences is crucial for improving prevention, diagnosis, and treatment strategies. These results underscore the importance of tailored treatment strategies based on PFT in order to reduce gender related cardiovascular risk and platelet aggregation may be a suitable test.

PO031

CLINICAL SEVERITY OF THE FIRST EPISODE AND RISK OF RECURRENT NEUROLOGICAL SYMPTOMS IN RELAPSES AMONG PATIENTS WITH IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background: Immune-mediated acquired thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy often characterized by neurological symptoms (NS) at onset. It is unclear whether NS are associated with a more severe disease course and if patients with NS at onset are at higher risk of experiencing NS at relapses.
Aims: To compare disease severity parameters in patients with and without NS at iTTP onset and to assess the recurrence of NS in subsequent relapses.
Methods: A cohort-study using data from the Milan TTP Registry, including patients at their 1st acute iTTP event was conducted. We excluded patients with previous ischemic stroke, patients with only headache as NS, and patients treated with caplacizumab for its influence on acute event outcomes.
Results: One-hundred patients were enrolled, 67 with NS and 33 without NS at onset of the 1st episode. The median age was slightly higher in the NS than in those without (44 *vs* 34). NS presence at onset was not associated with abnormal laboratory findings, plasmapheresis sessions, need for early rituximab, and exacerbations. Cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and previous major cardiovascular events, were more common in patients with NS, although without statistical significance (Table 1). During a median follow-up time of 8 years (IQR 4, 12), 14 out of 30 patients with NS at the 1st episode (47%), and none of the 15 patients without-NS had a recurrence of NS at relapse, 4 of whom with ischemic strokes (Table 1).
Conclusions: Our study suggests that the presence of NS is not a risk factor of disease severity. However, patients displaying NS at their 1st episode are at a higher risk of experiencing NS also during relapses, hence exhibiting a more severe phenotype. This pattern suggests an underlying, individual-specific risk factor influencing disease expression that remains to be elucidated.

Table 1.

Main patients and iTTP related features

Variables	With Neurological symptoms (n=67)	Without neurological symptoms (n=33)	Difference of medians/proportions (95% CI)
Female, n (%)	48 (72)	25 (76)	4.6 (-14.8, 27.8)
Age at episode (years), median (IQR)	44 (30, 53)	34 (28, 51)	4 (-3, 11)
Platelet count (x10^3/uL), median (IQR)[1]	11.5 (8, 20)	13 (9, 21)	-1 (-4, 2)
Hemoglobin, g/dL, median (IQR)[2]	8.0 (7.1, 9.1)	8.9 (7.3, 10.1)	-0.7 (-1.5, 2.0)
LDH (U/L), median (IQR)[3]	1101 (722, 1731)	1634 (914, 2195)	-312.5 (-712, 69)
Number of PEX sessions, median (IQR)[4]	13.5 (9, 22)	12 (7, 20)	2 (-2, 6)
Rituximab added to PEX, n (%)	19 (28.4)	6 (18.2)	12.0 (-12.0, 30.3)
Exacerbation, n (%)	12 (17.9)	5 (14.7)	5.1 (-23.2, 26.4)
Hypertension, n (%)	11 (16.4)	1 (3.1)	28.3 (-5.4, 41.5)
Diabetes, n (%)	3 (4.5)	0 (0)	34.0 (-35.6, 44.9)
Obesity, n (%)	11 (16.4)	8 (24.2)	11.2 (-14.5, 35.1)
Smoking, n (%)[5]	30 (46)	16 (50)	4.6 (-14.7, 24.0)
Hyperlipidemia, n (%)[6]	9 (13.4)	2 (6.1)	16.7 (-18.7, 35.2)
Previous MACE, n (%)[7]	6 (9)	0 (0)	35.5 (-9.4, 46.2)
Clinical Relapse, n (%)[8]	30 (50)	15 (46)	17.5 (-2.9, 35.7)
Neurological symptoms at relapse, n(%)[9]	14 (47)	0 (0)	48.4 (16.2, 66.6)

[1]available in 92 patients (64 with NS, 32 without); [2]available in 97 patients (65 with NS, 32 without); [3]available in 83 patients (57 with NS, 26 without); [4]available in 89 patients (60 with NS, 29 without); [5]available in 98 patients (65 with NS, 33 without); [6]available 99 patients (67 with NS, 32 without). [7]Major cardiovascular events (MACEs: 2 myocardial infarction, 4 transitory ischemic attack. [8]available in 60 patients, 7 lost to follow up. Median follow-up time and iTTP relapses: 7 years (IQR 4, 12) and 2 iTTP relapses (IQR 1, 3) for patients with NS; 8 years (IQR 6, 12) and 3 iTTP relapses (IQR 1, 6) for patients without NS. For patients with more than one iTTP relapse, symptoms of each episode have been checked.
[9] 4 patients have had an ischemic stroke at relapse.

PO032

CLINICAL CHARACTERISTICS AND MANAGEMENT OF ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA: DATA FROM A SINGLE-CENTRE EXPERIENCE

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Background: Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare disease mediated by autoantibodies blocking ADAMTS13, the von Willebrand Factor (vWF)-cleaving protease.
Aims: To evaluate the clinical-laboratory characteristics

of aTTP patients at time of first diagnosis, relapse,and remission.
Methods: In this retrospective study, we analyzed medical records of patients with aTTP diagnosis, defined by low ADAMTS13 activity (<10%) and detection of anti-ADAMTS13 autoantibodies, who were hospitalized in our Institute from January 2010 to December 2022.
Results: Eleven subjects with aTTP were identified (6/5-females/males, median age at onset 54 years). Three subjects had clinical relapses for a total of 17 aTTP acute events (9 first events and 8 relapses). Organ damage was characterized by neurological, cardiac, and mucocutaneous involvement, which was more common at first diagnosis than at relapse (7/9vs4/8, 5/9vs2/8, 5/9vs2/8, respectively). No first event but 3 relapses had only laboratory findings of thrombocytopenia and microangiopathic haemolytic anaemia. In all the 17 events PLASMIC score was ≥5. Beyond plasma exchange and immunosuppression, 6 events were treated with caplacizumab, the anti-vWF nanobody, which was associated with a reduced number of plasma-exchanges to achieve clinical response (median 7vs16) and a shorter hospital stay (median 23vs29days). No death was observed. Three subjects had biochemical relapses, *i.e.* reduction of ADAMTS13 activity without thrombotic microangiopathy, and were treated successfully with rituximab (n=2) or corticosteroids (n=1). During the intercritical periods of remission, subjects with relapses had lower levels and higher variance of ADAMTS13 activity than those without relapses (49±30%vs78±18%, P<0.001).
Conclusions: The data of this small study support the use of PLASMIC score as diagnostic tool and caplacizumab as therapeutic agent in aTTP, as well as the role of ADAMTS13 activity monitoring during remission and the use of rituximab in biochemical relapses. The development of large multicentric registers with adequate statistical power is eagerly needed.

PO033

IMMUNE THROMBOCYTOPENIA: EFFICACY AND SAFETY ON THE COMBINED USE OF FOSTAMATINIB AND TPO RECEPTOR AGONIST

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Background and Aims: The treatment landscape for immune thrombocytopenia (ITP) has expanded in recent years. For second line of treatment, clinicians have several drugs available such as thrombopoietin receptor agonist (TPOra) and a syk inhibitor, fostamatinib (FOS). The last one was approved by EMA in January 2020 for the treatment of adults with chronic ITP with insufficient response to previous treatments. However, because of prescriptive limits and relatively recent approval, data supporting safety and efficacy of this clinical practice are actually lacking.
Methods: Data of patients (pts) affected by chronic ITP treated with FOS associated with TPOra between January 2022 and April 2024 was retrospectively collected and analyzed. Response (R) and complete response (CR) was defined in accordance with the FIT study.
Results: A total of 15 pts have received FOS in our Center, in 8 pts (53%) FOS was used in combination with TPOra (eltrombopag in 5 pts, romiplostim in 2 pts and avatrombopag in 1 pts) in order to stop the last one at the end of tapering period. 4/8 (50%) were women and mean age was 61,1 years (range 86-20). Three pts are suffering from hypertension, 1 had ischemic stroke in 2020, 2 have a thromboembolism history and 1 suffers from peripheral arterial disease. 2/8 pts were on antiplatelet therapy and 1/8 on direct oral anticoagulant (DOAC). 5 pts (63%) started FOS for loss of response to TPOra, 1 pts for elevated thrombotic risk and 2 pts (25%) for both conditions. At the start of FOS, median previous treatment for ITP was 2,5 (range 2-4) 1 pts was splenectomized; 100% of pts had been exposed to at least one TPOra, 25% to rituximab and 1 pts to vincristine. The median exposure to TPOra before starting FOS was 28 months (range 4-106). Mean platelet count was 18.000 x 109/L (pts with loss of response) and median ITP duration was 11,5 years (range 1-30). At the time of data collection, the dose of FOS was 150 mg bid for 2 pts and 100 mg bid for 6 pts. After starting FOS 3 pts needed one rescue therapy, median time to R was 6 days for 7 pts (1 pts have not reached R) and median time to CR was 8 days for 6 pts (2 pts have not reached CR). Four pts start TPOra decalage; 1 of them discontinued TPOra in CR, 3 pts not discontinued TPOra because loss of response. One pts discontinued FOS for uncontrolled hypertension. The median follow-up time undergoing FOS plus TPOra was 71,5 days (range 587-27). Two pts experienced diarrhea that not required treatment discontinuation, nor transaminitis neither thrombotic events were observed.
Conclusions: In our experience combination of TPOra plus FOS has showed to be effective and safe both in relapse and increased thrombotic risk setting. In addition, a shorter time to response was observed than in the FIT study, which could be explained by the synergy of the mechanism of action of TPOra and FOS. Certainly, there is a need for these results to be validated by larger case series and studies.

PO034

UPDATE ON ITP PATIENTS TREATED WITH AVATROMBOPAG: A REAL-LIFE MONOCENTRIC EXPERIENCE

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Background and Aims: Avatrombopag (AVA), a second-generation thrombopoietin receptor agonist (TPO-RA), is part of the second-line treatment of chronic idiopathic thrombocytopenic purpura (ITP). Post-hoc analyses of the Phase III study showed that patients (pts) younger, males and pts with fewer than three prior ITP therapies had longer treatment responses. In addition, prior use of TPO-RAs such as eltrombopag and romiplostim had a minimal effect on durability of response.
The aim of this study was to evaluate the efficacy and treatment duration of AVA in pts with ITP treated at our centre in a real-world setting.
Materials and Methods: We performed a retrospective analysis of data from a single-centre cohort of 21 ITP pts (15 women, 6 men) with a median age of 55 years (24-79) at the start of AVA therapy. All pts were in the chronic phase of their ITP. The median plt count at baseline was 34000/μL (1000-146000/μL). Blood samples were taken weekly during the first month of treatment and then at variable intervals depending on the plt count. Data were collected between August 2022 and April 2024.
Results: After one week of treatment, the median plt value was 89000/μL (1000-1000000/μL); the median time to reach a plt count higher than baseline was 7 days (5-21). 3 pts (14%) never reached a plt count>50000/μL. The starting dose of AVA was 20 mg/die. At 1 month, only 5 pts (24%) were on concomitant therapy.
16 pts (76%) switched from another TPO-RA to AVA for different reasons: 7 (43%) loss of response, 3 (19%) no response (NR), 3 (19%) pts preference, 3 (19%) adverse events (AE). 9 pts (43%) received both first generation TPO-RAs. After one month of treatment, we observed no difference in terms of response (PLT>50000/μL) between pts with less or more than 50 years (p=0.67) and in pts treated with >or ≤3 previous lines (p=0.6); or between males and females (p=0.33). No differences were observed even between pts with plt values more or less than 15000/μL at the start of AVA (p=1) or between pts with more or less than 30000/μL at the start of AVA (p=0.38). Treatment was discontinued in 8 pts (38%): 6 (28%) NR, 1 (5%) fluctuating plt values, 1 (5%) AE. 3 pts (14%) had to be temporarily stopped because of thrombocytosis. Currently 13 pts (62%) are on AVA with a median duration of therapy of 314 days (30-621), in particular 8 pts at a dosage lower than 20 mg/die; median number of tablets/weekly taken is 4 (2-21).
Conclusions: In our analysis demonstrate the efficacy of AVA with a durable response despite multiple previous treatments including other TPO-RAs. Moreover, the efficacy is confirmed by the possibility to reduce the dose of the drug.

PO035

LONG TERM USE OF CAPLACIZUMAB IN IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background and Aims: Immune-mediated Thrombotic Thrombocytopenic Purpura (iTTP) is a rare hematological emergency due to a ADAMTS13 deficiency and anti-ADAMTS13 antibodies. The gold standard of treatment is plasma exchange, immunosuppression and Caplacizumab (CPL). Phase 2 and 3 studies have shown that CPL significantly reduces time to platelet count normalization and rate of refractoriness, recurrences and death during treatment. CPL is generally administered until ADAMTS13 activity is restored, however the data sheet reports treatment times up to 65 days. No reports on safety and efficacy are available for longer treatment.
Methods: Data on 12 patients (pts) affected by iTTP, followed at the Hematology Department of Molinette Hospital in Turin and Santa Croce e Carle Hospital in Cuneo between 2021 and 2024, was retrospectively collected and analyzed. Pts were divided in Short-Term group (STg) if they had received CPL <65 days (5 pts) and in Long-Term group (LTg) if they had received CPL >65 days (7 pts).
Results: 9/12 pts were treated with CPL for a first episode of iPTT, 3/12 were treated for a iPTT relapse (they hadn't received CPL before). At the initial presentation, patients had a PLASMIC score between 5 and 7. In 2 LTg pts, CPL had been discontinued early but due to failure to maintain clinical remission was reintroduced after a few days, therefore total days were counted. To date, 2 pts in the LTg have not reached drug interruption. Characteristics of pts are summarized in Table 1. Comparing the two groups, it can be seen that, on average, platelets and hemoglobin at diagnosis were 18000/μl - 8.9 g/dl in the STg and 10000/μl - 7.7 g/dl in the LTg, respectively; the mean value of LDH was 1019 IU/l in STg and 1468 IU/l in LTg; the mean value of ADAMTS13 inhibitors was 23 BU/ml in STg and 100 BU/ml in LTg; the number of PEX performed was, on average, 4 in the STg and 5 in the LTg. Rituximab (RTX) was administered to 2/5 pts (40%) in the STg, and to 7/7 pts (100%) in the LTg. Additional therapies were required in no pts (0%) in the STg and in 2/7 pts

(28,6%) in the LTg (cyclophosphamide and/or bortezomib). At least one bleeding event (BE) occurred in 2/5 pts (40%) in the STg and in 5/7 pts (71,4%) in the LTg, among them there was only 1 major bleeding in STg. In the STg, BE were hematoma at coaxial catheter implantation and melena with anemia (major bleeding). In the LTg, in the first 2 months of CPL, BE were nosebleed, ecchymosis at the injection site and small spontaneous ecchymosis, while after 2 months of CPL were nosebleed, ecchymosis at the injection site and an episode of metrorrhagia. No further effects on clinical efficacy possibly linked to the presence of neutralizing antibody (ADA) were noted in LTg.

Conclusions: In our cohort, CPL shows to be effective and safe even when used for >65 days. With the limitation of low sample size, at diagnosis LTg has platelets count and hemoglobin levels lower than STg although not significantly, further ADAMTS13 inhibitor title is significantly higher in LTg than in STg as well as the RTX use. These might be elements that could help us in predicting the response to treatment. Indeed, CPL has changed the treatment paradigm but criteria are therefore needed to improve the natural history of the disease, to personalize therapy and to obtain the best cost-effective solution.

Table 1.

Patient's Characteristics

	Short Term group	Long Term group	P. overall
Age at diagnosis (years)	67.0 [62.0;70.0]	43.0 [37.5;56.5]	**0.028**
Gender	Male 0 (0.00%) Female 5 (100%)	Male 2 (28.6%) Female 5 (71.4%)	0.470
Days in Caplacizumab	32.0 [30.0;32.0]	109 [85.5;146]	**0.004**
ADAMTS13 inhibitor at diagnosis (BU/ml)	23.0 [17.0;51.0]	100 [80.0;122]	**0.015**
ADAMTS13 activity at diagnosis (IU/ml)	0.01 [0.01;0.01]	0.01 [0.01;0.02]	0.428
Plt at diagnosis (/µl)	18000 [9000;51000]	10000 [8500;13000]	0.414
Hb at diagnosis (g/dl)	8.90 [7.60;9.50]	7.70 [6.95;8.15]	0.255
LDH at diagnosis (IU/l)	1019 [590;2013]	1468 [1394;2558]	0.372
PEX number	4.00 [4.00;4.00]	5.00 [4.50;5.50]	0.059
Administration of RTX	Yes 2 (40.0%) No 3 (60.0%)	Yes 7 (100%) No 0 (0.00%)	**0.045**
Additional therapy*	Yes 0 (0.00%) No 5 (100%)	Yes 2 (28.6%) No 5 (71.4%)	0.470
All bleeding	Yes 2 (40.0%) No 3 (60.0%)	Yes 5 (71.4%) No 2 (28.6%)	0.558
Major bleeding	Yes 1 (20.0%) No 4 (80.0%)	Yes 0 (0.00%) No 7 (100.0%)	

*cyclophosphamide and/or bortezomib
BU/ml: Bethesda Unit/milliliters; IU/ml: International Unit/milliliters; Plt: platelet count; µl: microliter; Hb: hemoglobin; g/dl: gram/deciliter; LDH: Lactate Dehydrogenase; IU/l: International Units/liter; PEX: plasma exchange; RTX: Rituximab.

PO036

REAL WORLD DATA ON THE IMPACT OF CAPLACIZUMAB IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA

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Introduction: Caplacizumab (CPL) is a monoclonal antibody approved for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP), both as first-line and subsequent lines of treatments. This study aimed to evaluate the advantages of CPL with reference to hospital length of stay and number of plasma exchanges (PEX) needed in real life.

Patients and Methods: The study cohort comprises 13 patients (6 males, 7 females, median age 42 years), treated for aTTP at our department in the last ten years. Three were terated with CPL at diagnosis, 4 during relapse, and 6 were never treated with CPL as their diagnosis was made before 2019. All patients were hospitalized at diagnosis, and some required additional admissions. The aim of our analysis was to compare patients who received CPL as first-line therapy, in addition to PEX, with those who never received it or received CPL in subsequent lines, in terms of relapses, evaluating the PEX required to achieve an initial platelet count of at least $100*10^3/\mu L$, the PEX needed to achieve remission, and the duration of hospital stay.

Results: The mean maximum length of hospital stay for patients treated with CPL as first line was 17 (14-21) days, while for patients treated in subsequent lines or not treated, it hospital stay lasted 21 (11-36) days. The mean number of PEX required to achieve remission at the last relapse for patients treated in the first line was 6 (4-10), while for patients treated in subsequent lines or not treated, it was 8 (4-21). The mean number of PEX required to achieve an initial platelet count of at least $100*10^3/\mu L$ for patients treated in the first line was 6 (4-10), while for patients treated in subsequent lines or not treated, it was 7 (4-9).

Conclusions: The analysis, conducted at a Regional Reference Center for the diagnosis and treatment of aTTP, confirms in a real life setting a reduction in the number of PEX required to achieve complete remission and duration of hospital stay after the availability of CPL ,compared to the pre- CPL era, as well as a shorter hospital stay when CPL is adopted as first-line therapy.

PO037

ANTIPHOSPHOLIPID AND IN PARTICULAR ANTI-PHOSPHATIDYLSERINE/PROTHROMBIN ANTIBODIES IDENTIFY A DISTINCT FORM OF ITP WITH OVERLAPPING FEATURES OF APS

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Background and Aims: Antiphospholipid syndrome (APS) and immune thrombocytopenia (ITP) are two distinct autoimmune diseases, however they may be closely related. ITP can be secondary to APS. On the other hand, thrombocytopenia is one of the clinical diagnostic criteria for APS. In addition to clinical domains, the diagnosis of APS consists of testing for lupus anticoagulant (LA), IgG and IgM anti-cardiolipin (aCL) and anti-beta2-glycoprotein I (aB2GP1) antibodies. There are also extra-criteria aPL, such as IgG and IgM anti-phosphatidylserine/prothrombin (aPS/PT) antibodies, that are acknowledged as supplementary markers for APS and they could play a crucial role, particularly in patients who test negative for conventional antibodies. This report examines the frequency of conventional and extra-critical antiphospholipid antibodies in a cohort of patients with ITP, focusing on the clinical features of these patients.
Methods: We analyzed a cohort of 88 patients with a diagnosis of ITP and 17 with a diagnosis of APS and thrombocytopenia. The IgG and IgM for aCL, aB2GPI and aPS/PT antibodies were detected by ELISA. LA was tested with two different reagents, used as screening and confirmatory tests (Silica Clotting Time and dRVVT Screen and Confirm), following the ISTH guidelines.
Results: The ITP cohort consisted of 88 patients, 78.4% were classified as primary ITP. 60 were tested for conventional antiphospholipid antibodies (LA, IgG and IgM aCL, and aB2GPI) and 21.7% were found to be aPL positive. Interestingly, a sub-cohort of 40 patients was also tested for aPS/PT antibodies and 5 patients (12.5%) were positive: all were positive for IgM aPS/PT and only one was positive for both IgG e and IgM aPS/PT. Of these, 2 were positive for both conventional aPL and aPS/PT antibodies and 3 were positive for aPS/PT antibodies only.
Comparing ITP patients with aPL positivity (considering both traditional and extra-criteria aPL) with those aPL-negative, a difference was observed in the degree of thrombocytopenia. aPL negative patients developed severe thrombocytopenia more frequently than aPL positive patients (68.2% *vs* 35.7% p=0.018). Subsequently, we considered a cohort of 17 patients with a concomitant diagnosis of APS and thrombocytopenia. Assessing the frequency of aPS/PT antibodies, 12/16 patients (75%) were positive for aPS/PT (including 46.7% IgG and 60% IgM). In terms of platelet count, only 11.8% of the patients had severe thrombocytopenia. In conclusion, there are three different entities of ITP: aPL-negative patients, aPL-positive patients and those with a concomitant diagnosis of APS and ITP. They differed in the degree of thrombocytopenia: APS patients had a higher platelet count than aPL-positive ITP patients (43895/μL±21947 *vs.* 26714/μL±15711 p=0.026) and than those aPL negative (43895/μL±21947 *vs* 19932/μL±21213 p<0.01). Consequently, APS patients required specific therapy for thrombocytopenia less frequently than aPL-positive and aPL-negative patients (57.9% *vs.* 72.2% *vs.* 88.6%, p=0.022).
Conclusions: The determination of traditional aPL and aPS/PT antibodies is of significant importance in the diagnostic workup of ITP patients, as it allows for the identification of a potential subgroup of patients with a distinct form of ITP. This subgroup does not meet the other clinical criteria for the diagnosis of APS, but they have different clinical features compared with the other forms of ITP.

P0038

CLINICAL FEATURES AND OUTCOMES IN IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA: A REPORT FROM A SINGLE COHORT OF PATIENTS OF AN INTERNAL MEDICINE CENTER

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Backgrounds and Aims: Thrombotic thrombocytopenic purpura is a potentially life-threatening form of thrombotic microangiopathy which results from a decrease or absence of the enzyme ADAMTS13 activity. A tempestive initiation of therapy can reduce morbidity and mortality. Due to disease physiopathology, characterized by relapses and remission, a periodic follow-up becomes fundamental with the aim to prevent, identify and treat potential relapses. In this study we analysed a large cohort of patients with TTP to describe their clinical features, treatments and outcomes, in order to draw some recommendations for their best management.
Methods: 43 patients with PTT with a 24-months follow-up were included in this study. In all these patients, we collected disease-relevant data, both in acute phase and periodic follow-up, including laboratory parameters, disease duration, number of relapses, hospitalization period, treatments.
Results: The population presents a median age of 54 years, 73% patients are female, 43% had at least one relapse during follow-up with a median time of 44 months. During acute phase 25 of 43 patients were treated with PEX and steroids, 18 of 43 also with Rituximab (RTX) and 5 also with Caplacizumab. Median hospital duration was 28,3 days in the group treated with RTX and 25,7 days in the group with Caplacizumab; these numbers differ significantly (p=0.004) from the 21,3 days in the group not treated with RTX and/or Caplacizumab. Median number of PEX sessions is 15,2 in the group of patients treated with RTX *vs* 11,5 of the group of patients untreated (p=0.007). Patients treated with RTX present a relapse median time of 50 months, which differs non statistically from the median time (44

months) of the patients untreated. 5 patients (12%) were treated with immunosuppressive prophylaxis with RTX and didn't develop short-term relapses (within 12 months). 12% of patients maintained low ADAMTS13 activity levels and persistence of autoantibodies without presenting any relapse in the last 5 years, contrary to what was expected (1.1 relapse/5 years).
Conclusions: Blood test results show the typical acute phase thrombotic microangiopathy pattern. More than a half of patients during the acute phase was treated with PEX and steroids, reserving use of RTX and Caplacizumab in patients nonresponding to the first line therapy, resulting in a major number of PEX sessions and longer hospital stay in this subgroup of patients. RTX in the acute phase showed efficacy in determining a clinical improvement and in the prevention of short-term relapses, without however increasing the median remission time. A subgroup of patients which, during follow-up, showed ADAMTS13 activity reduction associated with positive antibodies titer and altered haemolysis parameters was treated with prophylactic RTX therapy and didn't develop short-term relapses. On the other hand, a subgroup of patients with permanent low ADAMTS activity levels and positive autoantibodies titer, without any suggestive haemolysis alteration, didn't show relapse although any prophylactic immunosuppressive therapy. The appropriate role of prophylactic treatment with RTX in the management of patients with asymptomatic severe ADAMTS13 deficiency remains uncertain; further investigations will be needed to identify additional parameters that can support the decision to give this treatment for this indication.

PO039

PROPHYLACTIC USE OF DANAPAROID AFTER LIVER TRANSPLANT IN HEPARIN-INDUCED THROMBOCYTOPENIA (HIT): A CASE REPORT

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Background: Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder of platelet activation caused by pathogenic antibodies against a platelet factor 4 (PF4)-heparin complex. It is the most frequent drug-induced immune thrombocytopenia and may lead to life threatening thrombosis. The diagnosis of HIT is based on an algorithm in which the first step is the evaluation of clinical pre-test probability (4T-score) which must be confirmed by an immunoassay (ELISA) and, if available, a functional test. The cornerstone of HIT management is to minimize the thrombotic risk. In all cases of suspected or proven HIT, any form of heparin should be avoided and an anti-coagulation therapy with an alternate drug is necessary. Current options include parent formulations such as argatobran and recently danaparoid also received approval for the treatment of HIT in the datasheet. Furthermore danaparoid is the first drug approved for use on prophylaxis (750 U twice daily) in patients at thrombotic risk with previous HIT.
Case Report: We report a case in which was used Danaparoid at prophylactic dose in a non-conventional way. A 63-year-old patient with previous hemorrhagic stroke, hypertension, a treated HCC and liver cirrhosis requiring TIPS placement, had an acute myocardial infarction complicated by two episodes of cardiac arrest. PTCA was subsequently performed and dual antiplatelet therapy and LMWH at prophylactic dose (4000U daily) was started. From initial values of 124.000/mmc platelets, a progressive thrombocytopenia was observed (nadir 39.000/mmc) until 4T-score was performed (5-intermediate probability) and heparin/PF4 antibody positivity was found (first positivity 10/08/22-last positivity 9/9/22). A switch from LMWH to fondaparinux (2.5mg daily) was opted for. Following the finding of DVT, the dosage of fondaparinux was increased to 7.5mg. At 1-month follow-up, the DVT had resolved, but given the need for anticoagulant therapy to maintain flow in the TIPS in anticipation of liver transplantation (LT), a switch to a treatment with DAPT+Warfarin and then a single antiplatelets approach was adopted as long term prophylaxis. Due to the intermediate probability of HIT and the high thrombotic perioperative risk (LT with mesenterico-portal anastomosis using interposition venous graft), LMWH therapy was not administered during surgery on 12/27/23. Instead, immediately after LT, antithrombotic prophylaxis with danaparoid (750U twice daily) was started and continued for 30 days. On surgical indication, prophylaxis was continued for another two months with fondaparinux (2.5 mg daily) and, at the end of two months, acetylsalicylic acid (75 mg daily) was started. During follow-up, there were no thrombohemobolic complications while there was a progressive recovery of platelet levels (at last check 138,000/mmc).
Conclusions: We report the first case of successful and prolonged use of danaparoid at prophylactic dose (750 U twice daily) in prevention of thrombotic complications after LT in a patient with previous diagnosis of HIT.

PO040

CONGENITAL RARE THROMBOFILIC DISORDER AND DEEP VENOUS THROMBOSIS IN A YOUNG WOMAN: A CASE REPORT

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Background: Homocystinuria (HCU) is a rare autosomal recessive disorder due to cystathionine B-syntase (CBS) deficiency in methionine metabolism . Late onset disease occurs with clinic manifestations including thromboembolic events . The incidence of venous thromboembolism (VTE) in homocystinuric untreated patients may be as high as 10% per year and VTE episodes occur in association of major or minor transient risk factors. We report of a case of deep vein thrombosis (DVT) associated HCU treatment with direct oral anticoagulant (DOAC).

Case Report: We report a case of a female patient of 28-years-old referred to our Angiology Unit complaining pain and tenderness in her right leg. She was on a estrogen-progestogen drug for contraceptive purposes. Compression ultrasound sonography revealed femoral-popliteal venous thrombosis. The patients was initially treated with low molecular weight heparin and then switched to rivaroxaban at standard dose. The thrombophilic study revealed very high homocysteine values (211 microm/l). The molecular analysis on genomic DNA identified heterozygosity of variants c.833T>C and c.111G>A in regions of the CBS gene. Both variants have already been described and are associated with HCU. The biochemical finding also revealed the presence of two heterozygous variants of MTHFR (C677T and A1298C). Vitamin supplementation was initiated. Only few case reports described the efficacy and safety of DOACs for the treatment of VTE associated with metabolic disorders but none in association with HCU. After the standard treatment period, rivaroxaban was continued at 10 mg OD, once the target of homocysteinemia values close to the upper limits of the normal. During the follow-up period (12 months), the patient did not experience thrombotic recurrences and bleeding events.

Conclusions: We described the case of DVT associated to HCU treated with rivaroxaban. This therapeutic approach it's not supported by suitable scientific evidence in this setting and further studies are needed.

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PO041

CONGENITAL HYPO-DYSFIBRINOGENEMIA: OUR EXPERIENCE WITH A POPLITEAL ARTERIAL OCCLUSION

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Background: Hypo-dysfibrinogenemia is a rare disease characterized by reduced antigenic level of fibrinogen associated with low functional activity. The diagnosis is based on the relationship between the activity and antigenic levels of fibrinogen. Molecular anomalies such as missense mutations in exon 2 of FGA and exon 8 of FGG lead to defects in the conversion of fibrinogen to fibrin

Case Report: A 60-year-old man came to our medical department with pain in the right lower limb and claudication less than 200 meters, on arterial ECD he presented with a complete popliteal occlusion with a good collateral circulation. The clinical history included previous TIA and cerebral gliosis, ulcerative colitis, congenital hypo-dysfibrinogenemia with heterozygous missense mutation c.952G>T in exon 8 of the FGG gene. The patient's treatment in the acute phase was LMWH and acetylsalicylic acid associated with intravenous treatment with iloprost. In the follow-up the patient is being treated with warfarin and acetylsalicylic acid with bimonthly infusions of Iloprost. The response to treatment was optimal with significant improvement in claudication (Figure 1).

Conclusions: The patient's mutation destabilizes fibrinogen, which is not expressed in plasma and its plasma half-life is extremely short. Due to the rarity of hypo-dysfibrinogenemia and the consequent absence of controlled studies, the clinical management of the patient derives from expert consensus. Any treatment considered in patients should first be based on personal and family history.

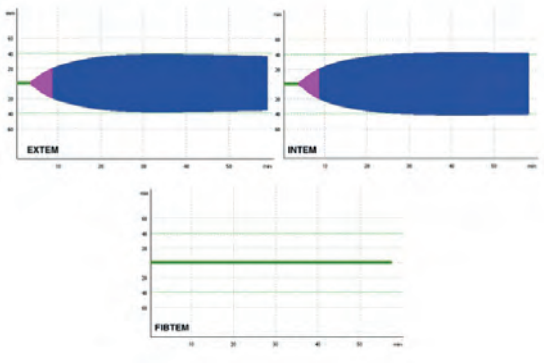

Figure 1.

PO042

DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH VENOUS THROMBOEMBOLISM AND SEVERE INHERITED THROMBOPHILIA

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Introduction: The role of direct oral anticoagulants (DOAC) in the management of patients with venous thromboembolism (VTE) and severe inherited thrombophilia is controversial.
Patients and Methods: We evaluated 56 consecutive patients (28 M, 28 F; age at first event 40.4±14.9 years) with a history of VTE [deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] and severe thrombophilia [AT, PS, PC deficiency, FV Leiden (FVL) homozygosis, FIIG20210A homozygosis, combined heterozygosis of FVL+ FIIG20210A, and homocystinuria], referred between March 2014 and April 2024 to 3 Centers: Thrombotic Unit, Ospedale del Mare, Naples; Department of Clinical Medicine and Surgery, Federico II University, Naples; and UOC Medicina Interna, AORN Moscati, Avellino. All patients were treated with DOAC (rivaroxaban, edoxaban, apixaban) for at least 3 months. Each patient underwent clinical/instrumental/laboratory follow-up every 3 months.
Results: In our setting of 56 patients, we identified: 6 AT deficiencies, 2 PC deficiencies, 11 PS deficiencies, 24 combined heterozygosis for FV Leiden+FII20210A, 5 FVL homozygosis, 6 FII20210A homozygosis, 1 combined heterozygosis FVL+homozygosis FII 20210A+PS deficiency, and 2 patients with homocystinuria. All patients received long-term anticoagulation: 16 patients switched from warfarin to DOAC, and 40 patients were treated with DOAC, as first line therapy. Thirty-three patients received long-term rivaroxaban (of them 6 with reduced 10 mg daily dose), 9 edoxaban, and 14 apixaban (of them 6 with reduced dose: 2.5 mg twice daily). One patient presented VTE during treatment with 20 mg rivaroxaban for atrial fibrillation and was then switched to full dose apixaban. One patient had spontaneous intracranial bleeding during warfarin treatment and was successfully switched to long term apixaban at low dose. Provoking factors (surgery, trauma, estrogens, COVID-19, cancer, immobilization, hospitalization) were present in 33.9% of cases, the others (66.1%) were unprovoked. Patients were treated for 1772±952.4 days (mean). During this time, no recurrences nor major bleedings were observed. We observed 2 cases of minor bleeding (both with 20 mg rivaroxaban): one patient suffered by microhematuria and gingival bleeding, and one patient presented occult blood in the stool with sigmoid polyposis, both patients had normal creatinine, normal body weight and normal PT and PTT, and were successfully treated with local measures. No differences for sex, type of thrombophilia, or drug were observed.
Conclusions: This study suggests that DOAC are an appropriate and safe option for treatment/secondary prophylaxis of VTE in severe hereditary thrombophilia. During the observation, in our setting, no thrombotic recurrences or major bleedings were observed.

PO043

THE RISK OF RECURRENT VENOUS THROMBOEMBOLISM IN PATIENTS WITH INHERITED THROMBOPHILIA IN ANTITHROMBOTIC PROPHYLAXIS WITH RIVAROXABAN 10MG/DAY: TWO CASES REPORT

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Background: The risk of recurrent thromboembolic disorders in the 10-year period following an episode of unprovoked venous thromboembolism (VTE) ranges between 30 and 50%. The risk factors of recurrence are the proximal location of VTE, obesity, old age and male sex, whereas the role of thrombophilia is controversial. In the recurrence a role is represented by post-baseline parameters such as the ultrasound assessment of residual vein thrombosis and the determination of D-dimer. While the latest international guidelines suggest long-term anticoagulation for most patients with the first episode of unprovoked VTE, new scenarios takes into consideration the identification of risk stratification models. A possible therapeutic choice is low-dose aspirin, which has recently been reported to decrease by more than 30% the risk of recurrent events, but the gold standard for the prevention of relapses is oral anticoagulant therapy represented by warfarin or the new direct oral anticoagulants (DOACs). Each DOAC has a different dosage schedule and dose modifications, with possible reductions, depending on patient-specific factors, including age, weight, renal function, serum creatinine, indication and concomitant medications. There are few clinical studies in the literature that evaluate individual variables in relation to the various doses used in therapy or prophylaxis.
Cases Report: We reported the clinical outcomes in two patients followed at our center in prophylactic treatment with rivaroxaban 10 mg/day after standard dose treatment for deep vein thrombosis (DVT). -The first patient (M.A.), male, is 63 years old, with previous 4 unprovoked DVT in the lower limbs. Came to our observation after the last episode of DVT and began treatment with rivaroxaban 20 mg/day for a total of 6 months, then 10 mg/day. Patient carrier of heterozygous Leiden factor. One month after the dose reduction, the patient presented an episode of superficial vein thrombosis (SVT). -The second patient (L.R.), female, is 55 years old, with two episodes of unprovoked SVT in 2022 and a spontaneous episode of DVT in 2023. In consideration of the clinical history and the S protein deficiency, after the full dose period with rivaroxaban 20 mg/day, she started prophylactic therapy with rivaroxaban 10 mg/day. A month later the appearance of a new event of SVT.
Conclusions: The patient carrying hereditary mutations of thrombophilia or deficiency of the main natural anticoagulants has a risk of developing recurrent thrombosis equal to 1,8 times compared to the normal population. The decision regarding the duration of anticoagulant treatment varies based on the characteristics of the indi-

vidual patient; evaluating personal medical history, any risk factors reported and the risk of bleeding. The two cases, although different, similar in terms of the incidence of a new thrombotic event which occurred during prophylactic therapy with rivaroxaban. Little scientific evidence in the literature on the superiority of one DOAC over another and no data on the long-term effectiveness of reduced dosages. It is necessary to collect a larger series of patients with thrombotic disorders and recurrent thrombosis during DOACs treatment.

PO044

WHAT THROMBOPHILIA SCREENING TESTS ARE INDICATED AND WHEN THEY SHOULD BE CONDUCTED: OUR EXPERIENCE

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Aims and Background: International literature agrees that some thrombophilia genetic testing are not indicated or even superfluous. For these reasons, it's necessary to determine the appropriateness of the use of such tests in clinical practice. The aim of this abstract was to understand if there is a significant relationship between some genetic variants and an increased risk of developing a deep vein thrombosis (DVT).
Methods: The current study was conducted on 1082 patients who visited the Departmental Operating Unit «Laboratory of Medical Genetics and Immunogenetics» of the «Madonna delle Grazie» Hospital in Matera from January 2022 to December 2023. Patients with a history of DVT (n=175) and patients with recurrent pregnancy loss (n=273) were used as case groups. Pregnant patients with a negative history of DVT (n=288) and patients undergoing IVF (*in vitro* assisted fertilization, n=346) were used as a control group. Patients with recurrent pregnancy loss were further divided into the following two subgroups: those with miscarriage in the first trimester of gestation and those with miscarriage in the second trimester. Genes and genetic variants studied were: c.1601G>A (p. Arg534Gln; commonly known as Factor V Leiden, historically reported as p. Arg506Gln); G20210A mutation in prothrombin gene (c.*97G>A); C677T and A1298C mutations in Methylene Tetrahydrofolate Reductase Gene (p. 222Ala>Val and p.429Glu>Ala). The method used was Real time PCR. The data obtained were analysed using ROC curve.
Results: Analysis of ROC curves shows that the C.1601G>A (p. Arg534Gln) variant in V Leiden increases the risk of thrombotic events (DVT/Pregnants AUC=0.94 and DVT/IVF AUC= 0.71) and of recurrent pregnancy loss in the first trimester (IT Miscarriages /Pregnants AUC= 0.94 and IT Miscarriages/IVF AUC=0.93) compared to the second trimester (IIT Miscarriages/Pregnants AUC= 0.54 and IIT Miscarriages/IVF AUC= 0.61). Similarly, the G20210A variant increases the risk of thrombotic events (DVT/Pregnants AUC=0.59 and DVT/IVF AUC=0.65) and recurrent pregnancy loss in the first trimester (IT Miscarriages/Pregnants AUC= 0.92 and IT Miscarriages/IVF AUC=0.93) compared to the second trimester of gestation (IIT Miscarriages /Pregnants AUC= 0.51 and IIT Miscarriages /IVF AUC= 0.60). On the other hand, the ROC curves of the A1298C and C677T variants in MTHFR gene are not significant.
Conclusions: Our data confirm what has already been reported in the literature that certain gene variants are associated with inherited thrombophilia. In particular, the study of c.1601G>A mutation in Factor V Leiden and of G20210A mutation in prothrombin are indicated in subjects with recurrent venous thrombosis and/or involving different vascular districts and in women with recurrent pregnancy loss, particularly in the first trimester. On the other hand, the study of the variants of the MTHFR gene has shown the absence of a predictive value of this test and that thrombotic risk is linked to hyperhomocysteinemia, a predictive marker of endothelial damage, that increases the possibility of the onset of a cardiovascular risk as consequence. For this reason, it is useful to carry out serum measurements of homocysteine, vitamins B9 (folic acid), B6 and B12. Genetic testing should be required to answer specific questions based on scientific evidence in the literature.

PO045

OXIDATIVE STRESS-INDUCED FIBRINOGEN MODIFICATIONS IN LIVER TRANSPLANT RECIPIENTS: UNRAVELING A NOVEL POTENTIAL MECHANISM OF THROMBOSIS

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Background and Aims: Cardiovascular events represent major cause of non–graft-related death after liver transplant. Evidence suggest that chronic inflammation associated to a remarkable oxidative stress in the presence of endothelial dysfunction and procoagulant environment play a major role in the promotion of thrombosis. However, the underlying pathogenetic mechanisms are unknown. In order to investigate the mechanisms of post-transplant thrombosis, the aim of the present study was to investigate the role of oxidation-induced structural and functional fibrinogen modifications in liver transplant recipients.

Methods: A case-control study was conducted on 40 clinically stable liver transplant recipients and 40 matched controls. Leukocyte ROS production, plasma lipid peroxidation, plasma glutathione content, plasma antioxidant capacity, fibrinogen oxidation, fibrinogen structural and functional features were compared between patients and controls.
Results: Patients displayed enhanced leukocyte ROS production and an increased plasma lipid peroxidation together with a reduced total antioxidant capacity compared to controls. This systemic oxidative stress resulted in fibrinogen oxidation and fibrinogen structural alterations. Thrombin-catalyzed fibrin polymerization and fibrin resistance to plasmin-induced lysis were significantly altered in patients respect to controls. Moreover, steatotic graft receivers and smoking habit were associated to reduced fibrin degradation rate.
Conclusions: ROS-induced fibrinogen structural changes could be related to increased thrombotic risk in liver transplant recipients.

PO046

POST-TRANSLATIONAL OXIDATIVE MODIFICATION OF FIBRINOGEN AND ITS ROLE IN THROMBOSIS: THE CASE OF ENDOMETRIOSIS

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Background and Aims: Endometriosis (EM) is a disorder of the female genital system defined as the presence of endometrial tissue outside the uterine cavity and characterized by an estrogen-dependent chronic inflammatory process and high cardiovascular risk. Inflammation and oxidative stress represent essential factors involved in the promotion of thrombosis, however, its underlying pathogenetic mechanisms are still unknown. On these bases, fibrinogen from patients and controls was purified and its structure and function were explored. Moreover, plasma redox status in EM women and age-matched healthy controls was assayed, in order to elucidate the possible mechanisms responsible for the increased cardiovascular risk in EM.
Methods: 15 EM women and 15 age-matched healthy controls were included in the study. Plasma lipid peroxidation, plasma total antioxidant capacity, purified fibrinogen structural and functional features were compared between patients and controls. In addition, fibrinogen oxidation, thrombin-catalyzed fibrinogen polymerization and fibrin resistance to plasmin-induced lysis were explored.
Results: The obtained results on EM patients clearly indicate an overall impaired redox balance, witnessed by increased plasma lipid peroxidation levels and reduced plasma TAC compared to healthy controls. Fibrinogen purified from EM women compared to controls displayed an increase in di-tyrosine content, a reduced susceptibility to plasmin-induced lysis and a slower rate of fibrin clot formation. As regards as fibrinogen structure, circular dichroism and intrinsic fluorescence spectroscopy experiments showed an altered fibrinogen structure in patients compared to controls.
Conclusions: Fibrinogen structural and functional changes occurring in EM women and fibrinogen oxidative modifications are evident in EM patients and could be involved in high thrombosis tendency. Then, our results could provide a biologically link between oxidative fibrinogen modifications and mechanism of thrombosis in women with EM. Further studies will allow us to elucidate the molecular mechanism underlying thrombosis in EM women and to assess the potential benefits of a redox balancing therapy.

PO047

RUXOLITINIB (JAK INHIBITOR) REDUCES ROS-DRIVEN STRUCTURAL AND FUNCTIONAL FIBRINOGEN ALTERATIONS IN PRIMARY MYELOFIBROSIS PATIENTS

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Background and Aims: Primary myelofibrosis (PMF) is one of four JAK2 mutation-prevalent myeloproliferative neoplasms (MPNs), causing a dramatic decrease in erythropoiesis and angiogenesis. About 90% of PMF patients exhibit mutations in JAK2, CALR or MPL genes; in particular, JAK2 induces cytokine independence, constitutive STAT proteins activation and reactive oxygen species (ROS) accumulation within hematopoietic stem cells, indicating oxidative stress as a factor implicated in PMF pathogenesis. As in many other diseases, inflammation and ROS are considered potential triggers of thrombotic events, which, in MPN diseases, represent the main cause of morbidity and mortality. Fibrinogen has been repeatedly suggested to play a multifaceted role in inflammatory responses and autoimmunity. In particular, in MPN patients, an

impaired fibrinolysis associated to endothelial cell dysfunction and increased production of ROS and proinflammatory cytokines have been reported. Consequently, in order to elucidate the mechanisms of thrombosis in PMF patients, we investigated the role of oxidation-induced structural and functional changes in fibrinogen purified from PMF patients and healthy controls. The effects of Ruxolitinib, a first-in-class JAK inhibitor, were also evaluated.

Methods: 20 PMF patients and 30 age- and sex-matched healthy control subjects were included in the study. Plasma redox status and fibrinogen structural and functional features were estimated in patients (pre *vs* post Ruxolitinib treatment) and controls.

Results: PMF patients displayed an altered systemic redox balance as indicated by significantly increased plasma lipid peroxidation and nitrate/nitrite levels and significantly reduced total antioxidant capacity and free thiol content. This oxidative impairment resulted in a sustained fibrinogen oxidation (*i.e.* dityrosine content) with marked alterations in fibrinogen secondary and tertiary structure (*i.e.* intrinsic fluorescence and far-UV circular dichroism). Structural alterations paralleled a remarkable fibrinogen functional impairment, with a significantly reduced ability to polymerize into fibrin and a lower fibrin susceptibility to plasmin-induced lysis. A positive correlation between fibrin resistance to plasmin digestion and plasma oxidative stress, as well as fibrinogen structural and functional alterations was observed. Additionally, significant correlations among fibrinogen structural and functional parameters, fibrin polymerization data and markers of redox status were observed. In patients receiving Ruxolitinib, significant improvements in redox status, fibrinogen structural and functional features were observed.

Conclusions: The reported findings show that in PMF patients oxidative stress is associated to structural and functional fibrinogen modifications, thus suggesting a possible pathogenetic mechanism of vascular events in PMF. Furthermore, the preliminary results about Ruxolitinib indicate that this treatment could be useful for its redox-balancing effect and cardiovascular prevention in these patients.

PO048

ADVANCING THROMBOSIS RESEARCH: A NOVEL DEVICE FOR MEASURING CLOT PERMEABILITY

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Background and Aims: Thromboembolism, a global leading cause of mortality, needs accurate risk assessment for effective prophylaxis and treatment. Current stratification methods fall short in predicting thrombotic events, emphasizing the need for a deeper understanding of clot properties. Fibrin clot permeability a crucial parameter in hypercoagulable states, is related to clot structure and thrombotic risk. Current clot permeability measurement limitations force the need for standardized methods, but call for improvements and more precise, repeatable, and standardized methods. Based on this background, our study presents a new device designed to measure blood clot permeability.

Methods: This system utilizes pressure-based approach in line with Darcy's law, offering heightened precision in identifying clot permeability. This device furnishes a valuable tool for assessing thrombotic risk, promising improved diagnostics and targeted therapeutic strategies.

Results: By permeability measurements on plasma or fibrin clots using specialized holders, this device demonstrates high accuracy and rapid results, holding potential to significantly enhance patient outcomes in cardiovascular diseases and associated pathologies. Permeability measures between clots from fibrinogen purified from high cardiovascular risk patients (n=20) and from age- and sex-matched controls (n=20) have been assessed. Our results show a significant difference between patient and control fibrin clot permeability (0.0487±0.0170 d *vs* 0.1200 ±0.0376 d, p<0.005), in line with the data reported in current literature.

Conclusions: In summary, our study introduces a novel device for measuring clot permeability, addressing the critical need for improved risk assessment and treatment of thromboembolism. By utilizing a pressure-based approach aligned with Darcy's law, this device offers heightened precision in identifying clot properties. Through automation of permeability measurements, it promises improved diagnostics and targeted therapeutic strategies, with the potential to significantly enhance patient outcomes in cardiovascular diseases and related pathologies. Moving forward, further validation and refinement of this device could contribute to standardized methods for assessing clot permeability, ultimately advancing the field of thromboembolism management and patient care.

PO049

THE EPIDEMIOLOGY OF ANTIPHOSPHOLIPID SYNDROME: THE IMPACT OF GENDER ON CLINICAL MANIFESTATIONS

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Background: Sntiphospholipid syndrome (APS) is an

autoimmune disease characterized by vascular (arterial and/or venous) thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). It requires the presence of a clinical criterion, either a vascular thrombosis or pregnancy morbidity, and a laboratory criterion, based on measurements of persistent aPL on two or more occasions, at least 12 weeks apart. The types of aPL accepted for the laboratory criterion include the lupus anticoagulant (LAC), anticardiolipin (aCL) IgG and IgM, and anti–β2-glycoprotein I (anti-β2GPI) IgG and IgM antibodies.

Aims: The aim of the study was to determine the clinical differences at diagnosis and during follow-up between male and female patients with primary APS.

Methods: We retrospectively studied 114 PAPS patients, according to Sapporo criteria, diagnosed and followed between 1998 and 2022, attending exclusively the outpatient clinics from the Haemostasis Centre, Moscati Hospital of Avellino, with at least five years of follow-up. The mean age at diagnosis was 36.4+11 years in males and 41.7+11 years in females. The follow-up after diagnosis was 8.7+3.1 years in males and 9.2+2.9 years in females.

Results: From the 114 patients studied, 48 were males and 66 females. There was a total of 73 patients with venous (39 male, 34 female) thrombotic events, 28 with arterial (16 male, 12 female), and 13 with 'mixed' thrombosis (arterial and venous) (7 male, 6 female). We observed a significant prevalence of stroke in females. In contrast, we found a significant prevalence of severe gastrointestinal complications in male compared to female patients (Figure 1).

Conclusions: Our findings show that clinical course in patients with PAPS may be different with significant prevalence of central nervous system involvement in females and gastrointestinal involvement in males. Factors such as accelerated atherosclerosis, hormones, related to gender could be the explanation of these findings.

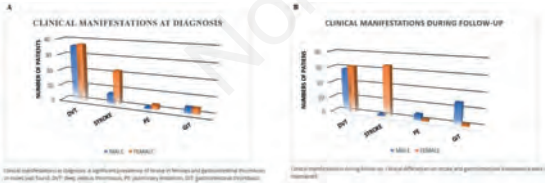

Figure 1.

PO050

MULTICENTER REGISTRY OF INTERNAL JUGULAR VEIN THROMBOSIS: A PRELIMINARY REPORT

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Background and Aims: Internal jugular vein (IJV) thrombosis is a potentially life-threating disease, due to the development of an intraluminal thrombus. The thrombosis can occur at any level, from the jugular foramen to the junction between the IJV and the subclavian vein, constituting the brachiocephalic vein. Serious life-threatening complications have been described following IJVthr, such as pulmonary embolism (PE).

Methods: We created a prospective multicenter registry on cases of jugular venous thrombosis from January 2024. We collected demographic, anthropometric, pathological anamnesis, pharmacological anamnesis, data on antithrombotic prophylaxis and therapy and presence of device. Data on clinical outcomes such as 30-day mortality, bleeding, and recurrence/extension of thrombosis were also collected. Data are presented as number and percentage.

Results: We found 13 cases of IJV thrombosis. The mean age of the patients was 67 years; 5 female (38.4%). Three (23%) patients were admitted to the ICU; 2 patients (15.3%) from the oncology service; 8 patients (61.5%) from the department of internal medicine. As regards the associated comorbidities, in 3 cases there was sepsis (23%); 2 cases of diabetes (15.3%); 8 cases of arterial hypertension (61.5%); 2 previous cases of stroke (15.3%); in 5 cases there was an active tumor (38.4%) and in 3 cases metastatic (23%); 2 cases of ischemic heart disease; 1 case of drug addiction. None of the patients had chronic venous disease, previous deep vein thrombosis or pulmonary embolism. In 10 cases (76.9%) the affected side was the right one. Only in 3 cases there was an isolated thrombosis of the IJV (23%); in 7 cases (53.8%) the jugular thrombosis originated from a superficial thrombosis of the arm (basilica or cephalic). In 3 cases the thrombosis developed from the subclavian (23%). In 10 cases thrombosis was associated with a device or recent placement of the same (76.9%) (3 from CVC; 7 from PICC or Midline). In 10 cases, IJV thrombosis was treated with LMWH in the acute phase (76.9%); three cases were not treated in the acute phase (23%). There were 3 cases in which post-acute phase aspirin was inserted (23%). Two deaths were recorded at 30 days (15.3%); one case of PE (7.6%). As regards bleeding, there was only one case of cerebral hemorrhage before the diagnosis of thrombosis; two cases of bleeding post-introduction of anticoagulant therapy, one minor and one major arising from a tumor mass.

Conclusions: From the data of our registry, the greatest number of cases of IJV thrombosis are detected in internal medicine wards. Arterial hypertension and the presence of an active tumor are the major associated comorbidities. No case was associated with previous DVT/PE, thus suggesting a pathogenesis other than that of «usual» thromboembolism. In most cases, the affected side is the right one, and thromboses are associated with device placement. The treatment of choice in the acute phase was based on low molecular weight heparin.

PO051

DIRECT ORAL ANTICOAGULANTS IN DEEP VEIN THROMBOSIS ASSOCIATED WITH INFERIOR VENA CAVA AGENESIS: A REPORT OF THREE CASES AND A SYSTEMATIC REVIEW

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Background and Aims: Inferior vena cava agenesis (IVCA) is a rare vascular abnormality characterised by the absence of one or more segments of the inferior vena cava and represents an underestimated cause of deep vein thrombosis (DVT). Given the very low prevalence of this condition and the lack of clinical trials, there is no consensus about the optimal anticoagulation strategy in IVCA-associated DVT. We aimed to investigate the effectiveness and the safety of DOACs in IVCA-associated DVT, especially in the extended phase treatment.
Methods: We described three patients with IVCA-associated DVT followed at our Institution and treated with DOACs. Then, we performed a systematic review of the literature for ICVA-associated DVT treated with DOACs in the last ten years.
Results: In addition to our 3 cases, we found data from 19 publications for a total of 30 patients with IVCA-associated DVT treated with DOACs (24 subjects treated with rivaroxaban, 8 with apixaban, and one with dabigatran). Most patients were males (72,7%) with a median age at DVT onset of 26.0 years (min-max range 13-64 years). The majority of DVT events were unprovoked (76%). The standard thrombophilia tests were mainly negative. The median follow-up period during DOAC therapy was 1.0 years (min-max range 0-10 years), with one splanchnic vein thrombosis reported and no haemorrhagic events. Table 1 summarises the clinical characteristics and outcomes of the cases included in the systematic review.

Table 1.

	All cases	DOAC full dose	DOAC prophylactic dose	Dose not reported
Patients, n	33	12	11	10
DOAC				
- rivaroxaban	24	10	7	7
- apixaban	8	1	4	3
- dabigatran	1	1	/	/
Male sex (%)	72.7	83.3	63.6	70.0
Age at first DVT, years (min-max)	26 (13-64)	24.5 (13-48)	20 (17-64)	33.5 (19-47)
Mean follow-up, years (min-max)	1.0 (0-10)	1.5 (0-10)	2.0 (0-7)	1.0 (0-1)
Thromboembolic recurrence, n	1	/	/	1
Bleedings, n	0	0	0	0
Thrombotic recurrences, n	1	0	0	1

Summary of the clinical characteristics and outcomes of the cases included in the systematic review by the dose of DOAC administered. n: number; DOAC: direct oral anticoagulant; full dose: rivaroxaban 20 mg once daily, apixaban 5 mg two times a day, dabigatran 150 mg two times a day; prophylactic dose: rivaroxaban 10 mg once daily, apixaban 2.5 mg two times a day

Conclusions: IVCA is a rare cause of DVT, which should be suspected in young adults with unprovoked DVT. Available data support the use of DOACs in IVCA-associated DVT, with a reassuring efficacy and safety profile.

PO052

CEREBRAL MAGNETIC RESONANCE IMAGING AND SINGLE-PHOTON EMISSION TOMOGRAPHY IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background and Aims: Antiphospholipid syndrome (APS) is characterized by the development of pregnancy morbidity, venous thromboembolism (VTE), transient ischemic attacks and stroke. Involvement of the central nervous system in APS can be evaluated by several radiological procedures. Magnetic resonance imaging (MRI) is often used for showing focal or diffuse brain ischemic lesions. Single-photon emission tomography (SPECT) has been used for the assessment of regional cerebral blood flow (rCBF). In this study we investigated a group of patients with APS using MRI and analysing changes in rCBF on a voxel basis using the Statistical Parametric Mapping (SPM) method.
Methods: This is a cohort study including 25 patients with APS diagnosed according to the 2006 revised criteria. Each patient underwent brain MRI and CT-ECD SPECT and a complete antiphospholipid laboratory profile. All the patients were on oral anticoagulation therapy and were routinely followed at our Haemostasis and Thrombosis Unit. On the basis of their clinical history, the patients were divided into two groups: the first one (group 1) included 11 patients with ischemic stroke while the second (group 2) included 14 patients with VTE. Images of cerebral MRI were categorized as normal (grade 0), with focal (grade 1), multifocal, or bilateral (grade 2) alterations. TC-ECD SPECT data were evaluated with SPM99 software.
Results: As regard the 25 patients included in the study, 18 (72%) were women and 7 (24%) were men. Mean age was 48+12 years. In group 1, MRI showed 5 and 6 patients with grade 1 and grade 2 brain alterations, respectively. In group 2, only 4 patients had grade 1 brain alterations while the other 10 patients did not show brain lesions. Perfusion SPECT showed a significant decrease in rCBF in all patients. Forty-five percent (5/11) of group 1 and, surprisingly, 86% (12/14) of group 2 showed severe cerebral hypoperfusion with 4 or more affected brain areas. In particular, in group 2 a significant

decrease in rCBF was identified in thalamus, cerebellum, frontal lobe and basal ganglia, while in group 1 a significant decreased in rCBF was found in parietal, occipital and temporal lobes (Figure 1). Regarding the laboratory profile of APS, triple positivity was found in 9 patients with VTE and in 10 patients with ischemic stroke. The severity of cerebral hypoperfusion in the two groups of patients did not correlate with either the laboratory profile of APS or the duration of the disease.

Conclusions: The absence of neurological involvement detected by MRI does not exclude an alteration of rCBF in APS. Brain SPECT analysis may be useful in patients with negative MRI, especially in those with VTE. Finally, in the absence of clinical criteria for APS and positive laboratory profile, a possible association between rCBF alterations and the clinical outcomes of APS should be investigated.

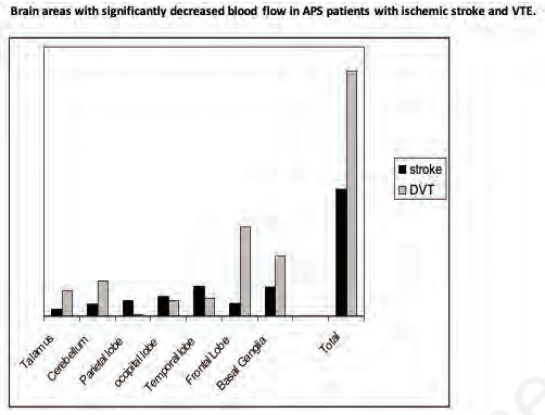

Figure 1.

PO053

USE OF DIRECT ORAL ANTICOAGULANTS IN CATHETER-RELATED THROMBOSIS: A SINGLE CENTRE EXPERIENCE

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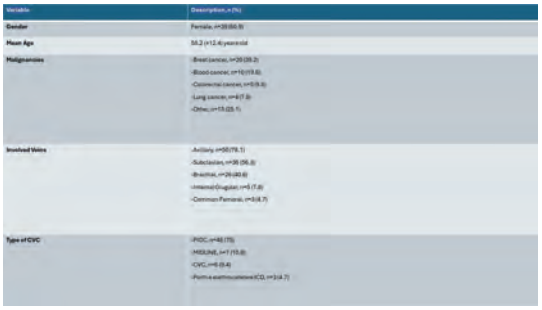
Background and Aims: Central venous Catheter-Related Thrombosis (CRT) is one of the major complications of the placement of these devices. According to international guidelines, recommended therapy involves low molecular weight heparin (LMWH) with or without bridging to warfarin. Although widely used as the standard of care for venous thromboembolism (VTE), as far as we know, literature about the use of direct oral anticoagulants (DOACs) in patients with CRT is still lacking. With this study we want to assess efficacy and safety of DOACs in patients with CRT.

Patients and Methods: We conducted an observational non-interventional study including consecutive patients ≥18 years of age with documented CRT treated with DOACs between December 1, 2020 and September 5, 2023 at Padova University Hospital (Angiology Unit). Patients who started medication with DOACs after more than 45 days since the diagnosis of CRT or patients with isolated superficial vein thrombosis were excluded. Documentation of thrombosis by compression ultrasonography or computed tomography (CT) scan was required. A 3-month follow up was performed for all patients during anticoagulant therapy and up to 3 months after discontinuation of DOACs. The efficacy outcome of this study was a composite of progression of CRT during treatment with DOACs or recurrence of VTE at 30 days after discontinuation of DOACs. The safety outcome of this study was the incidence of major bleeding, clinically relevant non-major bleeding (CRNMB), minor bleeding and death from all causes. Continuous variables with a normal distribution were described as the mean (±standard deviation), while continuous variables with a skewed distribution were described as median value with interquartile range (IQR). Categorical variables are presented as frequencies and percentage.

Results: Fifty patients (29 women, 56.8%) with documented CRT were enrolled. Mean age was 57.1 (±2.12) years. In most patients (n=37, 74%) CVC was placed for chemotherapy. In 37 (74%) patients the main risk factor was active cancer, while in 12 (24%) patients there was no identifiable risk factor except the presence of the venous catheter. Types of active malignancy included breast cancer (n=13, 35.2%), followed by haematological (n=7, 18.9%) and colorectal cancer (n=4, 10.8%). Peripherally inserted central catheters (PICC) were most common (n=36, 72%), followed by midlines (n=6, 12%). The drug most commonly used was edoxaban (n=34, 68%), apixaban and rivaroxaban were used in 12 (24%) and 4 (8%) patients, respectively. During the follow-up, a progression of CRT occurred in 1 patient and no recurrent VTE was observed. Two patients (4%) experienced 4 total minor bleeding episodes during treatment with edoxaban, while no one experienced major bleeding or CRNMB events. There was one death due to progression of cancer in a patient with colorectal cancer (Table 1).

Table 1.



Conclusions: In our study, DOACs have shown to have a good tolerance with few minor bleeding events and only one recurrence.

PO054

ACUTE AND SUBACUTE PULMONARY CYANO-ACRYLATE GLUE EMBOLISM: TWO CLINICAL CASES OF A RARE COMPLICATION FOLLOWING VARICOCELE INTERVENTIONAL RADIOLOGY PROCEDURES

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Background: Evidence on epidemiology and treatment of pulmonary cyano-acrylate glue embolism (PGE) is anecdotal, but unwanted glue embolization is a possible complication of scleroembolization (SE) procedures, such as those widely diffused to treat varicocele. We present two cases of PGE following interventional radiology treatment referred to our Haemostasis Clinic.
Case Reports: Case 1: a 22-year-old male, with unremarkable medical history, underwent left spermatic vein SE for symptomatic varicocele. During the glue infusion, accidental reflux of the material occurred. Sudden drop in oxygen saturation and increase in the heart rate of the patient occurred, quickly resolving spontaneously. An angiographic study of the pulmonary arteries demonstrated peripheral opacities, mostly at the right superior lobe. Blood tests showed normal CBC count, coagulation, renal and hepatic function. The patient was referred to us and a 3-month antithrombotic therapy with rivaroxaban was prescribed. At the 3-month follow-up, the patient performed a chest contrast CT, and no embolic defects were displayed. The pulmonary parenchyma and the spirometry testing were normal as well, and the antithrombotic therapy was terminated. Case 2: a 28-year-old male presented with dyspnoea and acute chest pain at the ER. His medical history was significant for bilateral varicocele and 13 days before the symptoms onset he had undergone SE of the right spermatic vein. The thoracic ultrasound showed right basal thickening with pleural effusion. Blood tests showed inflammation and d-dimer elevation. The chest contrast CT manifested numerous millimetric markedly hyperdense endoluminal defects at the distal portion of the subsegmental branches of the pulmonary arteries bilaterally, associated with pulmonary infarctions. At the superior right lobe an 18 mm mold high-density clot was located between segmental arterial branches. The images were likely suggestive of glue emboli. Echocardiography displayed the absence of heart function impairment. LMWH was initiated, and the patient was referred to us. We proposed shift to oral therapy and prescribed 3-month antithrombotic treatment with rivaroxaban. The patient will soon be re-evaluated with a new chest contrast CT.
Conclusions: The migration of glue to pulmonary arteries occurring after pelvic SE is infrequent and descriptions in the literature are exceptional; but due to the diffusion of these procedures, the number may rise.
As shown from our reports, not only this complication may occur during the procedure, but also afterwards: it is important to suspect PGE when a patient presents with dyspnoea, chest pain, tachycardia, hypoxia, and has a history significant for SE treatment. Our decision of pursuing an antithrombotic therapy was based on various factors. First, we considered the non-resorbable and long-persisting nature of cyano-acrylate glue, which is a watery solution that polymerizes immediately when in contact with blood, and its ability of perpetuating local inflammation in the lung circulation and parenchyma. Second, we evaluated the symptomatic presentation of the embolism, the extension, and the presence of pulmonary infarction. Anticoagulation aims not to dissolve the embolus, rather to prevent endothelial damage, block the coagulation cascade, avoid pulmonary infarction or its progression. Further evidence, reports, and clinical practice guidelines are needed on this topic.

PO055

INHERITED THROMBOPHILIA IN A COHORT OF BETA-THALASSEMIA PATIENTS

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Background: The β-thalassemia (βT) syndromes are a group of inherited disorders of hemoglobin synthesis, characterized by various degrees of defective β-chain production. Several clinical complications involving the haemostatic balance have been described during the course of βT, they include pulmonary hypertension, venous thromboembolism (VTE) and thromboembolic events (TEE), with a prevalence ranging from 1.1% to 5.3%. The hypercoagulable state in βT patients is not completed understood but it has been attributed to several factors including a procoagulant phenotype of red blood cells, decreased levels of natural anticoagulants, enhanced platelets activation and endothelial damage. With reference to the coinheritance of genetic thrombophilia, it may also play an important role in the pathogenesis of a TEE in βT like for other diseases. Limited studies did not observe an increased frequency of thrombophilic mutations in βT patients, however there is not a sufficient, well-structured number of studies to draw firm conclusions.
Aims: A retrospective study was conducted with the objective to investigate the frequency of prescription of

genetic thrombophilia screening (FIIG20210A and FV Leiden) in our cohort of βT patients.

Methods: We performed a retrospective analysis of clinical history and hospital records of all patients undergo to genetic thrombophilia screening in the last 10 years (2013-2023) at our Reference Regional centre.

Results: Thirty-three patients with βT were identified from a total of 187 βT patients regularly followed-up at our centre. Twenty-one patients underwent splenectomy and 12 had a history of VTE (Table 1). None of the patients were homozygous FII (G20210A) or FV Leiden gene mutation, 1 of the 32 patients was heterozygous for the FII (G20210A) gene mutation (frequency of 3.1%) and 2 were heterozygous for FV Leiden (frequency of 6.25%). Thrombophilia genetic screening was found positive (heterozygous for FVL) in one of the 12 patients (8%) with a history of VTE. Our findings are in line with published data regarding frequencies of FII (G20210A) gene mutation (3.1 *vs* 3%) in βT patients while the frequencies of FVL resulted reduced (6.25 *vs* 11.5%). In our clinical practice, genetic thrombophilia screening is not part of the standard laboratory work-up of βT patients but it is mainly performed in presence of history of VTE or in patients candidate to splenectomy, to evaluate the thrombotic risk before surgery.

Table 1.

Characteristics of patients

Patients' characteristics	n=33
Age (median, IQR) years	47 (35-54)
Sex M/F	13/20
βTM / βTI	12/21
Comorbidity (n°/%)	
- Hypertension	2 (6)
- Cardiopathy	1 (3)
- Diabetes	2 (6)
- Pulmonary hypertension	3 (9)
- Hemocromatosis	24 (72)
- Liver disease	8 (24)
- Osteoporosis	17 (51)
- Hypothyroidism	4 (12)
βT therapy (n°/%)	
- Transfusion	22 (67)
- HU	6 (18)
- ICT	22 (67)
Genetic thrombophilia screening	33
- No mutations	30
- FVL*	2
- FII 20210A*	1
Splenectomy (n°/%)	21 (60)
VTE (n°/%)	12 (8)
- DVT-PE	4 (33)
- SVT	3 (25)
- Atipical-DVT	5 (41)

Abbreviation: βTM: β-thalassemia major; β-thalassemia intermedia; ICT: iron chelation therapy; HU:hydroxyurea; VTE: venous thromboembolism. DVT: deep vein thrombosis; PE: pulmonary embolism, SVT: superficial vein thrombosis. FV Leiden; *heterozygous

Conclusions: Prothrombotic gene mutations do not seem to play a crucial role in the pathogenesis of VTE in our cohort of patients. In clinical practice, inherited thrombophilia has been used as marker of thrombotic risk in patients candidate to splenectomy or with history of VTE. Identify the thrombotic profile of βT patients according to genetic thrombophilia screening may contribute to guide a tailored approach to prophylactic and long-term anticoagulant treatment, in absence of clear guidelines.

PO056

DIRECT ORAL ANTICOAGULANTS FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH BRAIN TUMOR

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Background and Aims: Brain tumors are at both high thrombotic and hemorrhagic risk. Therefore, anticoagulant treatment in these patients can be challenging. Clinical experience with direct oral anticoagulants (DOACs) in brain tumors patients is limited and low molecular weight heparin (LMWH) is suggested in those with brain metastases. We report our clinical experience on anticoagulant treatment for venous thromboembolism (VTE) in brain tumors patients.

Methods: In this case series, we report data on patients diagnosed with VTE with primary or metastatic brain tumor consecutively referred to our clinics and prescribed with both LMWH or DOACs. Data on clinical and radiological follow-up were collected approximately every 6-12 months according to scheduled visits.

Table 1.

PT N.	AGE (at diagnosis)	SEX	Primary/metastatic brain cancer	Anticoagulant treatment: drug and dosage	DURATION of TREATMENT (months)	Bleeding*
1	49	M	GBM IV	Apixaban 5 mg BID	9	/
2	76	F	Metastasis (breast cancer)	Enoxaparin 1 mg/kg BID	10	NMCR
3	58	F	Metastasis (breast cancer)	Apixaban 5 mg BID	16	/
4	83	F	Metastasis (colon cancer)	Apixaban 5 mg BID	3	Minor
5	75	F	Metastasis (unknown)	Edoxaban 30 mg OD	3	Major
6	64	M	Metastasis (lung cancer)	Edoxaban 60 mg OD	2	/
7	46	M	GBM	Enoxaparin 1 mg/kg BID	7	/
8	45	M	Metastasis (colon cancer)	Rivaroxaban 20 mg OD	11	/
9	53	M	GBM IV	Apixaban 5 mg BID	2	/
10	63	M	Metastasis (melanoma)	Apixaban 5 mg BID	2	/
11	49	M	astrocitoma	Xarelto 20 mg OD	48	/
12	64	F	Metastasis (breast cancer)	Edoxaban 60 mg OD	17	/
13	70	M	GBM	Edoxaban 60 mg OD	4	/
14	72	F	cordoma	Edoxaban 30 mg OD	12	/
15	54	M	GBM	Edoxaban 60 mg OD	4	Minor
16	74	M	cordoma	Edoxaban 60 mg OD	12	/
17	76	F	meningioma	Edoxaban 60 mg OD	7	/
18	85	F	meningioma	Edoxaban 60 mg OD	3	/
19	63	M	GBM	Apixaban 5 mg BID	1	/
20	77	M	meningioma	Edoxaban 60 mg OD	5	/
21	69	F	meningioma	Apixaban 5 mg BID	12	Minor
22	66	M	GBM	Apixaban 5 mg BID	12	/
23	52	M	oligodendroglioma	Apixaban 5 mg BID	5	Minor
24	80	F	Metastasis (endometrial cancer)	Enoxaparin 0.8 mg/Kg BID	5	/
25	69	F	meningioma	Enoxaparin 1 mg/kg BID	2	/
26	67	F	meningioma	Enoxaparin 1 mg/kg BID	1.5	/
27	66	M	GBM	Enoxaparin 1 mg/kg BID	6	/

*according to ISTH criteria; NMCR=non major clinically relevant

Results: Twenty-seven brain tumors patients were diagnosed with VTE. The mean age at enrollment was 65±11 years (range, 46-83); 15 patients (55.6%) were male. A lower limb deep vein thrombosis (DVT) was diagnosed in 14 patients (51.9%), while a pulmonary embolism was detected in 9 patients (33.3%); only 1 patient had a cere-

bral thrombosis diagnosed at the same time of cancer. Eighteen patients (66.6%) had primary brain tumors. DOACs were the preferred treatment for most of patients (21 patients, 77.8%); 18 patients received antiepileptic drugs together with a DOAC, with levetiracetam being the preferred drug (15/18); type and duration of anticoagulant treatment are detailed on the Table 1. During a period of anticoagulant treatment of 8±9 months (range 1-48 months), partial or complete recanalization of DVT was described in 15 patients (55.6%); major/non-major clinically relevant bleedings were recorded in 2 patients (7.4%), 1 treated with a DOAC and the other taking enoxaparin at the standard dose. All bleeding complications occurred in patients with brain metastases.

Conclusions: According to our experience, DOACs seem to be an effective and relatively safe option for the treatment of VTE in patients with brain tumors. Further investigations on this topic are needed.

PO057

CHARACTERISTICS AND OUTCOME OF 41 PATIENTS WITH ACQUIRED HEMOPHILIA A. AN 18 YEARS' EXPERIENCE

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Background and Aims: Acquired hemophilia A (AHA) is a rare autoimmune disease, whose incidence has been estimated to be 1.34-1.48/milion/year. It is characterized by the development of antibodies against coagulative factors, mainly Factor VIII. The onset of the disease may be dramatic exposing the patient to haemorrhagic shock or severe bleeding, with a mortality risk of between 3% and 9%. AHA is suspected in a patient with unprovoked bleeding, a negative personal and family history of haemorrhages, and a prolonged aPTT that is uncorrected after a mixing test with normal plasma. In AHA, a low FVIII level and the presence of FVIII inhibitor, detected based on the Bethesda methods, confirm the diagnosis.

Materials and Methods: Demographics, underlying disorders, bleeding characteristics, treatment, and outcome of a series of 41 AHA patients are recorded. Prothrombin time, activated partial thromboplastin time silica based, mixing test, FVIII one stage assay and inhibitor assay using the Bethesda method were carried out.

Results: Diagnosis and treatment were done in our Haemostasis and Thrombosis Unit between 2005 and 2023. The estimated incidence of AHA in our series is 2 cases per million/year (range from 0 to 5,4). The median age at diagnosis was 67,8 years (range 15-93). AHA idiopathic or associated to postpartum, autoimmune disease and cancer were diagnosed in 10 (24%), 4 (10%), 18 (44%) and 9 (22%) out of 41 patients, respectively. Diagnostic delay was more than 30 days in 15/41 cases (36,5%). A total of 38/41 (93%) patients showed spontaneous bleeding. The most common presentation is mucocutaneous bleed (23/41, 56%) (Table 1). Hemostatic bypassing therapy was started in all patients. Steroids were the most used immunosuppressive agent. Clinical remission was achieved in 100% patients. No patient died.

Conclusions: Our data show that a Haemostasis and Thrombosis Unit characterized by having the availability of a clinical ward, a second-level laboratory, and a dedicated ambulatory service can properly manage patients with AHA. This may be important to consider for obtaining an optimal patient care. The Italian Society for the Study of Hemostasis and Thrombosis (SISET) is undertaking a difficult task to obtain recognition for this figure that should be present in every hospital.

Table 1.

Main characteristics of patients with AHA

Severity of bleeding	
Major, n (%)	16 (39%)
Minor, n (%)	25 (61%)
Delayed of diagnosis	
>30 days n (%)	15 (36.6%)
7-30 days n (%)	21 (53.6%)
<7 days n (%)	4 (9.8%)
Causes of bleeding episodes	
Spontaneous n (%)	38 (93%)
Post-traumatic; post -surgery n (%)	3 (7%)
Sites of bleeding	
Ecchymosis n (%)	23 (56%)
Muscular haematomas n (%)	25 (61%)
Hemarthrosis n (%)	4 (10%)
Haemorrhagic bullae (%)	3 (7%)
Intraparenchymal bleeding n (%)	4 (10%)
Post-partum n (%)	4 (10%)
Gastrointestinal bleeding n (%)	3 (7%)

PO058

ACQUIRED VON WILLEBRAND DISEASE IN PATIENTS WITH MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

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Backgrounds and Aims: Acquired von Willebrand syndrome (AvWS) is a rare bleeding disorder associated with hematoproliferative disorders, autoimmune conditions, neoplasia and cardiovascular disorders that often present a diagnostic challenge. Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common causes of AvWS. MGUS-AvWD results from accelerated vWF clearance by monoclonal immunoglobulins (Ig). Consequently, standard treatment protocols for congenital vWD based on intermittent bolus dosing of vWF concentrates are often suboptimal because of inadequate peak response and profoundly reduced vWF half-life. AvWS typically presents as mucocutaneous bleeding in individuals with no personal or family history of bleeding disorder. To date, no standard treatment guidelines are available for this distinct and rare disorder. High-dose intravenous immunoglobulin (IVIG) is also effective with a slightly longer response duration, up to 3-4 weeks. Several studies evidenced how the antimyeloma treatment led to improvement or even normalization of AvWS, but the therapeutic approach in AvWS patients with MGUS or smouldering multiple myeloma without end-organ damage is less clear. The aim of this work is to report our experience about MGUS-AvWS and IVIG treatment.
Methods: We retrospectively analysed clinical and laboratory data of two patients with avWS due to MGUS and treated with 400 mcg/Kg of IVIG daily for 4 days: the first patient, a young man, diagnosed at the age of 26, after recurrent muscle hematomas and episodes of hematuria, is still treated with IVIG cycles every 4 weeks, because of an occupation at risk of trauma: he reports some bruising, especially during the 3rd week after the infusion, but he never reported any significant bleeding after 9 years since the diagnosis. The second patient, a 74-year-old man, did not have a history of bleedings, but he was treated once with IVIG to test the response in prevision of surgery.
Results: The IVIG were effective with a response duration of 3.5 weeks for the younger patient and of 5 weeks for the older one. The results are provided in Figure 1.

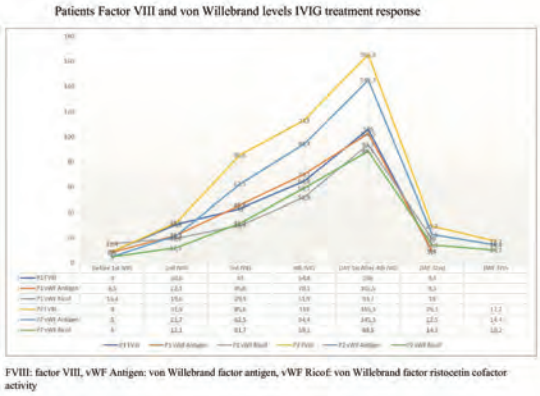

Figure 1.

Conclusions: Our results confirm what it is well known in literature: the use of IVIG alone for MGUS-avWS patients has been largely successful, with reported high response efficacy rates in case of bleeding and in the perioperative setting. However, given IVIG's delayed onset of action (elevation in FVIII and vWF concentrations observed within 24–48 h), it is generally recommended that IVIG be administered together with more immediatly acting therapies such as Desmopressin or vWF/FVIII concentrates

PO059

USE ON DEMAND OF EHLS IN MILD-TO-MODERATE HEMOPHILIA PATIENTS: A SINGLE CENTER EXPERIENCE

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Background and Aims: For patients (pts) affected by severe hemophilia A (HA) and B (HB), the use of extended half-life clotting factor concentrate (EHL CFC) is well established, both in the prophylaxis setting and for invasive procedures/surgery. In contrast, for patients with mild-to-moderate hemophilia, evidence is still limited. These patients could benefit from the use of EHL CFCs for the treatment of bleeding and pre- and post-surgical prophylaxis by maintaining prolonged hemostasis with a limited number of infusions.
Case Report: We report a case series of 8 pts affected by mild-to-moderate hemophilia and treated with an EHL CFC for surgery prophylaxis and for bleeding episodes (Table 1). Median age was 49 years (range 19-78), 1/8 was female, 3/8 suffers from HA and 5/8 suffers from HB. Mean basal FVIII was 10% (range 8-13), mean basal FIX was 11% (range 3-20) and all were treated on demand and were not sufficient at self-infusion. First pt arrived at our attention for right elbow hemarthrosis on Friday afternoon; pt was infused with EHL CFC in order to treat bleeding and avoid weekend hospital admission. Another infusion was performed after 72 h and resolution of hemarthrosis was observed. The pt returns 1 month later with hemorrhoidal bleeding and one EHL CFC infusion was performed with bleeding interruption. Three pts underwent dental extraction (plus implantology in 1 pts) with removal of stitches 7 days after surgery using a single EHL CFC infusion. Another pts for multiple dental extractions received 3 infusions every 72h of EHL CFC to ensure trough level above 20% for 1

week. This pt had the same procedure after DDAVP complicated by major bleeding a few months earlier. An esophagogastroduodenoscopy with biopsy was performed under EHL CFCs coverage in a woman affected by B hemophilia and erosive duodenitis, without complications. Left hip replacement was performed using an EHL CFC in a pt who had previously undergone knee replacement; a comparison between the two surgeries in terms of burden of infusion was made. Last pt had a left atrial appendage closure for atrial fibrillation with subsequent need for dual antiplatelet therapy (DAPT) for 1 month. In this period to achieve trough above 20% to allow DAPT was administered EHL CFC weekly. Nor hemorrhagic complications neither inhibitors were observed.

Conclusions: In conclusion in our case series, the use of EHL CFCs in patients affected by mild-to-moderate hemophilia A and B has been shown to be safe and effective, allowing reduction in intensity of care with fewer infusions compared to standard CFC. In pts who are not able to self-inject means a saving hospital access.

Table 1.

	Hemophilia (basal level)	*Type bleeding/surgery*	*N° of infusions (EHL CFC)*	*N° predicted infusions (SHL CFC)**	*FVIII trough*	*Inhibitors after EHL*
Case 1	HA (8%)	Right elbow hemarthrosis; hemorrhoids bleeding	2;1		9% (72h)	No
Case 2	HB (20%)	Gastroscopy with biopsy	1	2	30%	No
Case 3	HA (10%)	Multiple dental extraction and implantology	1	6	20%	No
Case 4	HB (6%)	Dental extraction and removal of stitches	1	4	21%	No
Case 5	HA (13%)	Multiple dental extraction	3	7	18%	No
Case 6	HB (14%)	Dental extraction and removal of stitches	1	3	20%	No
Case 7	HB (11%)	LAAC + DAPT	1/week	3/week	20%	No
Case 8	HB (3%)	Left hip replacement	15 (since D +40)	34 (since D +40)	50% (D 1-11) 20% (D 12-40)	No

EHL CFC: extended half-life clotting factor concentrate; SHL CFC: short half-life clotting factor concentrate; FVIII: factor VIII of coagulation; HA: hemophilia A; HB: hemophilia B; LAAC: Left atrial appendage closure; D: day. *According with World Federation of Hemophilia (WFH) guidelines for the management of hemophilia – 3rd Edition

PO060

POSTPARTUM-ACQUIRED HEMOPHILIA A MANAGEMENT: RETROSPECTIVE EVALUATION OF 15 CASES

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Backgrounds and Aims: Acquired Hemophilia A (AHA) is a rare and severe bleeding disorder caused by autoantibodies directed against coagulation factor VIII (FVIII), generally associated with pregnancy or in the elderly. The pattern of bleeding varies from mild bruising, diffuse muscle hematomas, and severe life-threatening intracranial or gastrointestinal bleeding. Spontaneous remission and prompt inhibitor eradication are described more frequently in postpartum patients. We evaluated retrospectively 15 postpartum AHA patients in order to evaluate clinical presentation and treatment response.

Methods: A retrospective multi-center study was conducted between 2007 and 2023 including 15 patients affected by postpartum AHA from 3 Hematology divisions in Sicily and Calabria.

Results: The median age at diagnosis was 31 years (range 24-38). All 15 patients reported bleeding episodes at presentation after a mean period of 40.6 days following delivery (range 2-180 days). In eleven patients (73.3%) the diagnosis occurred during the first month postpartum. As for the four patients with delayed onset, they were diagnosed after two, four, four and six months from delivery. Seven patients (46%) were primipara, while three of them had a history of abortion. Notably, five patients suffered from pre-existing autoimmune disorders. The medium level of FVIII was 4.42% (range 0-12.8%), with a medium FVIII-inhibitor titer of 35 BU (range 2-156 BU) using the Bethesda assay. The most severe bleeding symptoms were metrorrhagia and genital bleeding in nine patients (60%), one patient had important muscular hematoma, while the remaining five (33%) reported only cutaneous bleeding. Two patients received hysterectomy due to severe bleeding before diagnosis. All patients required anti-hemorrhagic therapy with a medium duration of 8 days (range 1-28 days): 60% (9/15) received eptacog alfa, one was treated with activated prothrombin complex concentrate, while both drugs were administered in combination in three of them (20%). The immunosuppressive treatment was steroids alone in nine patients, 27% (4/15) received azathioprine or cyclophosphamide in combination with prednisone, while in two patients rituximab immunotherapy was used following immunosuppressive combination therapy. After a medium period of 28 days (range 10-210 days), the anti-FVIII inhibitor was eradicated with normalization of the coagulation values in all but one patient, who is still on steroids one year following diagnosis. However, the duration of immunosuppressive therapy, including tapering, was significantly longer with a medium duration of 2.3 months (range 1-23 months). At cut-off data, all patients were alive and well at the last follow-up, without significant adverse events, except for one patient that experienced disease relapse three months following first episode and was successfully treated with rituximab.

Conclusions: Major bleeding was present in two-thirds of postpartum AHA patients and was successfully treated with bypassing agents. Postpartum AHA has been reported to have a high rate of spontaneous remission. However, nearly half of the population had inhibitor eradication more than one month after disease onset, using immunosuppressive treatment for more than 2 months, and additional drugs were used in 40% of them, evidencing difficulties in treatment remission in "so- called" favorable postpartum subpopulation.

PO061

MANAGEMENT OF SEVERE CORONARY ARTERY DISEASE IN TWO PERSONS WITH SEVERE HEMOPHILIA ON EMICIZUMAB PROPHYLAXIS

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Background: Cardiovascular disease (CVD) is an emerging medical issue in persons with hemophilia (PWH), whose life expectancy is now overlapping that of the unaffected peers. CVD management requires a careful balance between bleeding and thrombosis risk when using both procoagulant and anticoagulant treatments. Clinical practice recommendations have recently been published, but practical experience is still poor. We describe the management of coronary artery disease (CAD) in two males with severe hemophilia A (SHA) on emicizumab prophylaxis and treated with rFVIII on demand. Case report 1: A 52-year-old man with SHA, controlled HIV infection, cleared HCV infection and arterial hypertension, during physical activity had a cardiac arrest. After resuscitation, the ECG showed an elevated ST in V1-V3. Coronarography, performed using femoral access after antihemorrhagic prophylaxis with rFVIII 65 U/kg, showed a trivasal CAD. A percutanous coronary intervention (PCI) was unsuccessfully performed and dual antiplatelet therapy (DAPT) started, along with rFVIII 25 U every 12 hours to keep a trough >50U/dL. Multidisciplinary evaluation opted for surgical revascularization without extracorporeal circulation using triple coronary artery bypass graft (CABG). As to antihemorrhagic prophylaxis rFVIII 65 U/kg before the surgery and the beginning of systemic heparinization (1.5 mg/kg) was administered, then replacement treatment was aimed at maintaining factor level between 50-80 U/dL until day+28, when anticoagulant therapy was stopped. As to antithrombotic prophylaxis, Calciparin 5000 IU every 12 hours until day+28 and ASA100mg/day were used. As to bleeding complications, he had 3 post-traumatic hematomas (tongue/lower lip and rectal abdominal muscle from resuscitation maneuvers, a right inguinal hematoma from PCI). Case report 2: A 68-year-old man with SHA, controlled HIV infection, cleared HCV infection, arterial hypertension, diabetes mellitus, asymptomatic for heart disease, underwent ECG to start physical activity with evidence of altered ventricular repolarization in V2-V5. Coronarographic CT showed a trivasal CAD, confirmed by coronarography, performed using radial access after antihemorrhagic prophylaxis with rFVIII 65U/kg. Multidisciplinary evaluation opted for surgical revascularization without extracorporeal circulation using triple CABG. As to antihemorrhagic prophylaxis rFVIII 65U/kg before surgery and the beginning of systemic heparinization (1.5 mg/kg) was administered, then replacement treatment was aimed at maintaining factor level between 50-80 U/dL until day+28, when anticoagulant therapy was stopped. As to antithrombotic prophylaxis, Calciparin 5000 IU every 12 hours until day+28 and ASA100 mg/day were used. As to post-operative complications a pericardial effusion resolved with percutaneous drainage, and a hematoma at the site of safenectomy occurred. Both patients continued emicizumab and ASA100 mg/die, without bleeding, nor need for infusions of rFVIII.
Conclusions: Multidisciplinary management and close laboratory monitoring allowed the execution of two triple CABG without significant hemorrhagic and thrombotic complications in PWH on emicizumab prophylaxis and multiple comorbidities. For the long duration of DAPT with its hemorrhagic risk after PCI, surgical revascularization was the choice, since single-antiplatelet therapy can be continued in PWH on emicizumab prophylaxis, without the need of associating rFVIII concentrate.

PO062

EMICIZUMAB FOR CONTROL OF BLEEDING SYMPTOMS IN PATIENTS WITH ACQUIRED HEMOPHILIA A

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Background and Aims: Acquired Hemophilia A (AHA) is an autoimmune disorder due to autoantibodies against factor VIII (FVIII). While triggering cause eradication and immunosuppressive therapies can restore normal levels of FVIII, during the time needed to achieve the remission of the disease the patient remain exposed to a high risk of spontaneous bleeds. Treatment of bleeds includes high doses of human FVIII, bypassing agents and porcine FVIII (pFVIII). Recently, emicizumab was included In Italy among the available drugs, according to law 648/96, for patients (pts) resistant or with no indication to the other treatments.
Methods: We analysed safety and efficacy of emicizumab treatment in three pts affected by AHA with active follow up at our Centre.
Results: Pts were two men and one woman with median age 83 years old (range 65-87) affected by idiopathic AHA. At diagnosis, FVIII was <1% in all pts and median title of FVIII inhibitors 13 BU (range 5.8-2480). Two pts had inhibitors against pFVIII at diagnosis and one developed them after 12 doses of pFVIII. Bleeding symptoms

of pts with inhibitors against pFVIII were treated with >5 doses of recombinant activated factor VII (rFVIIa). All pts started immunosuppressive therapy with prednisone 1 mg/kg; in one pt cyclophosphamide and rituximab were also added due to very high inhibitor title. All pts had arterial hypertension; two pts also had additional cardiovascular risk factors including obesity, atrial fibrillation, type 2 diabetes, dyslipidaemia and ischemic cardiopathy. Emicizumab was started after a median of 39 days of hospitalization (median 3-49) due to recurrent bleeds despite rFVIIa treatment or loss of efficacy of pFVIII, with unstable haemoglobin levels. At beginning of emicizumab treatment, all pts still had FVIII levels <1% and median FVIII inhibitors 9.6 UB (range 9.3-720). Emicizumab loading dose used was 3 mg/kg at days 1 and 3, followed by 1.5 mg/kg weekly as maintaining dose. Median duration of hospitalization after the beginning of emicizumab treatment was 7 days (range 4-9). Both administrations of loading doses were performed in a in-hospital setting; one pt was discharged after the first maintenance dose. All pts had normalization of aPTT ratio before discharge (median 0.84, range 0.75-1.05), and continued follow up in an outpatient setting. Emicizumab was discontinued after a median of 55 days (range 42-160), once pts achieved FVIII levels greater than 50%. All pts continued immunosuppressive treatment. No bleeding events occurred during emicizumab treatment, nor thrombotic events or adverse events related to the drug. FVIII and inhibitors levels were monitored with one stage method before emicizumab and with chromogenic method during and after emicizumab treatment. After discontinuation of emicizumab, all pts continued immunosuppressive treatment until achievement of complete remission. Two pts had a relapse of inhibitors after steroid tapering, successfully managed with restart of low dose immunosuppression.

Conclusions: Emicizumab prophylaxis in pts with AHA allowed to control bleeds in case of inefficacy of rFVIIa and pFVIII, and to manage pts in an outpatient setting. No adverse events occurred, including thrombotic events, despite concomitant cardiovascular disorders. Emicizumab could be a useful tool to control bleeding symptoms during the first period of immunosuppressive treatment, although further studies are needed.

PO063

ASSESSMENT OF THE IMPACT OF THE "SIMPLE CARE" AND "HOME DELIVERY" PATIENT SOLUTIONS IN SEVERE HAEMOPHILIA A PATIENTS TREATED WITH EMICIZUMAB: A NATIONAL SURVEY ADDRESSING PATIENTS AND PHYSICIANS

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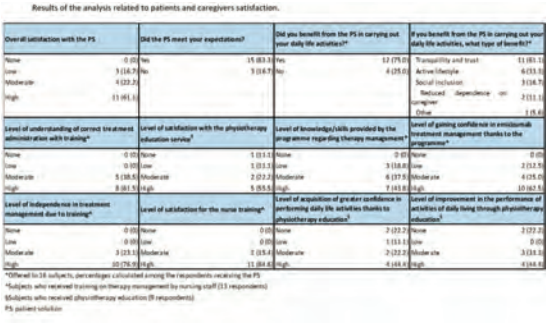
Background and Aims: Several home-based, patient support programs have been developed over the last few years in different clinical settings. The aim of our study was to explore the impact generated by the "Simple Care" and "Home Delivery" patient solutions on patients with severe Haemophilia A who recently started emicizumab treatment by using a survey addressed to patients, caregivers and physicians.

Methods: A qualitative survey was conducted involving 10 clinical centres, 18 subjects (11 patients, 7 caregivers) and 9 physicians. The data collection was performed between August 2022 - August 2023. The primary variables included were general satisfaction, educational impact, impact on daily activities, socio-economic value.

Results: The rate of response among patients and caregivers was 50.0% (18 respondents). The overall satisfaction towards the benefit of the patient solution, for knowledge and skills provided by the programme was moderate-to-high for more than 80% of subjects, 75% of respondents reported benefits in carrying out daily activities. Moderate-to-high level of understanding of the appropriate treatment administration modalities was reported by all subjects receiving training on therapy management by nursing staff. Six physicians reported moderate-to-high levels of satisfaction on the information received, and a low to no level of complexity of patient management through the patient solution (66.7%). A 100% moderate-to-high positive impact on patient adherence to treatment was expressed, as an 88.9% moderate-to-high positive impact on disease monitoring. Ninety-four percent of subjects decreased the number of visits to clinical centres after the start of the patient solution due to an improvement in the quality of care and reduced workload (Table 1).

Table 1.


Results of the analysis related to patients and caregivers satisfaction.

Overall satisfaction with the PS		Did the PS meet your expectations?		Did you benefit from the PS in carrying out your daily life activities?*		If you benefit from the PS in carrying out your daily life activities, what type of benefit?*	
None	0 (0)	Yes	15 (83.3)	Yes	12 (75.0)	Tranquility and trust	11 (81.1)
Low	3 (16.7)	No	3 (16.7)	No	4 (25.0)	Active lifestyle	6 (33.3)
Moderate	4 (22.2)					Social inclusion	3 (16.7)
High	11 (61.1)					Reduced dependence on caregiver	2 (11.1)
						Other	1 (5.6)
Level of understanding of correct treatment administration with training*		**Level of satisfaction with the physiotherapy education service†**		**Level of knowledge/skills provided by the programme regarding therapy management‡**		**Level of gaining confidence in emicizumab treatment management thanks to the programme***	
None	0 (0)	None	1 (11.1)	None	0 (0)	None	0 (0)
Low	0 (0)	Low	1 (11.1)	Low	3 (18.8)	Low	2 (12.5)
Moderate	5 (38.5)	Moderate	2 (22.2)	Moderate	6 (37.5)	Moderate	4 (25.0)
High	8 (61.5)	High	5 (55.5)	High	7 (43.8)	High	10 (62.5)
Level of independence in treatment management due to training*		**Level of satisfaction for the nurse training¶**		**Level of acquisition of greater confidence in performing daily life activities thanks to physiotherapy education‡**		**Level of improvement in the performance of activities of daily living through physiotherapy education‡**	
None	0 (0)	None	0 (0)	None	2 (22.2)	None	2 (22.2)
Low	0 (0)	Low	0 (0)	Low	1 (11.1)	Low	0 (0)
Moderate	3 (23.1)	Moderate	2 (15.4)	Moderate	2 (22.2)	Moderate	3 (16.7)
High	10 (76.9)	High	11 (84.6)	High	4 (44.4)	High	13 (72.2)

*Offered to 18 subjects, percentages calculated among the respondents receiving the PS
*Subjects who received training on therapy management by nursing staff (13 respondents)
†Subjects who received physiotherapy education (9 respondents)
PS: patient solution

Conclusions: Our survey shows that a patient solution aimed to provide educational training, physiotherapeutic support and psychological counselling resulted in an improvement of patients and caregivers satisfaction, in a positive evaluation by physicians and in positive impact on the overall management and social impact of the disease.

PO064

FACTORS RELATED TO ACQUIRED VON WILLEBRAND SYNDROME IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

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Background and Aims: Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that is similar to its inherited counterpart in terms of clinical and laboratory manifestations. Association between AVWS and myeloproliferative neoplasms (MPNs), mainly Essential thrombocythemia (ET) and Polycythemia vera (PV), has been widely described in presence of extreme thrombocytosis. The facilitated interaction between platelets factor receptor GPIb and VWF due to high platelet numbers, as seen in ET, permits the degradation of VWF resulting in low levels of VWF due to its accelerated removal from plasma by absorption onto malignant cells. Factors related to the development of AVWS are unclarified: in the literature mutational status has a controversial role in different cohorts and a defined platelet count predictive of this condition has not been established.
Methods: We retrospectively analyze data of 18 patients with MPN (13 ET, 5 PV) diagnosed and followed in our Department (12 M, 6 F, median age at MPN diagnosis 40,5 y, median follow-up 9,8 y), tested for suspected AVWS, on the basis of extreme thrombocytosis (>1000 x 10^9/L) or bleeding manifestations. For all patients we had complete clinical history and available mutational status (10 *CALR*, 7 *JAK2*V617F, 1 triple negative). We analyze results of 30 blood samples of these 18 patients, recording VWF antigen - VWF:Ag levels (normal 52-178%), ristocetin cofactor activity - VWF:RCoA (normal 46-178%), VWF:RCoA/VWF:Ag ratio and platelet count at time of VWF evaluation. 11 patients (61%) had at least one bleeding manifestation, 5 of these were major events (Table 1).
Results: Patients with *JAK2*V617F mutation (JAK-pos n=7, 39%) showed a tendency to have a higher hematocrit (49% *vs* 43%, p=ns) and a significantly lower platelet counts both at diagnosis (635±280 x 10^9/L *vs* 1170±403 x10^9/L, p= 0.02) and at time of VWF evaluation (1035±548 x 10^9/L *vs* 1418±529 x10^9/L, p= 0.04) compared to *JAK2* unmutated patients (JAK-neg: 10 *CALR*+1 triple negative). VWF:RCoA was moderately reduced than normal values (36%±27) in JAK2-pos while JAK2-neg showed a normal activity (49%±32). VWF:Ag levels were significantly higher in JAK-pos compared to JAK-neg (126%±64 *vs* 81%±30, p 0.03), furthermore, ratio was significantly lower in JAK-pos (p 0.04). JAK-pos tended to have a higher prevalence of bleedings (n=6, 85%) compared to JAK-neg (n=5, 45%); detailed description of bleeding manifestation is reported in Table 1.
Conclusions: It's known that patients with MPN are prone to develop AVWS in presence of extreme thrombocytosis although alterations in VWF parameters are also described in asymptomatic patients with platelet count <1000 ×10^9/L. We observed that patients with *JAK2* mutation have a significant reduction in VWF:RCoA/VWF:Ag ratio, secondary to an increase of antigen and to a moderate reduction of VWF:RCoA. Considering that JAK-pos patients display a tendency to more bleeding manifestations but an lower platet count compared to JAK-neg in presence of a only moderate VWF:RCoA reduction, our results suggest a central role of the presence of *JAK2*V617F mutation in bleeding diathesis with unclear mechanisms not necessary related to AVWS and/or extreme thrombocytosis. We aim to conduct further investigations, including platelet function and aggregation, on a larger series of patients with MPN, trying to define the pathophysiological basis of our observation.

Table 1.

	JAK2-POSITIVE (N=7)	JAK2-NEGATIVE (N=11)
AT LEAST ONE BLEEDING MANIFESTATION (N,%)	6 (85%)	5(45%)
MINOR BLEEDING (N, %)	2 (28%)	4 (36%)
EPISTAXIS	1 (14%)	2 (18%)
MUSCLE HEMATOMA	1 (14%)	0
GASTROINTESTINAL BLEEDING	0	1 (9%)
GUM BLEEDING	0	1 (9%)
MENORRHAGIA	0	0
MAJOR BLEEDING (N, %)	4 (57%)	1 (9%)
EPISTAXIS	0	0
MUSCLE HEMATOMA	2 (28.5%)	0
GASTROINTESTINAL BLEEDING	2 (28.5%)	0
GUM BLEEDING	0	0
MENORRHAGIA	0	1 (9%)

Bleeding manifestations in relation to JAK2 mutational status. Bleeding events were defined as 'major' or 'minor' according to the International Society on Thrombosis and Haemostasis definitions.

PO065

EFFICACY OF EMICIZUMAB IN THE MANAGEMENT OF SEVERE HEMOPHILIA A: A CASE REPORT OF SUCCESSFUL THERAPY IN A PATIENT UNRESPONSIVE TO CONVENTIONAL TREATMENTS

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Recent advancements in severe hemophilia management have seen a paradigm shift with the advent of new extended half-life (EHL) molecules and emicizumab, approved in 2017 for hemophilia A. Emicizumab, administered weekly or biweekly subcutaneously, has shown remarkable efficacy in reducing bleeding episodes, irrespective of inhibitors, offering a more convenient treatment option. The growing emphasis on quality of life in healthcare, underscores the psychological, social, and emotional toll chronic diseases like hemophilia impose on patients and their families. The case study presented

highlights the benefits of personalized therapies like tailored prophylaxis in enhancing the quality of life for hemophilic patients, considering the profound impact of hemophilia on various aspects of patients' lives. The case involves an 18-year-old male diagnosed with severe hemophilia A, with a history of unsuccessful inhibitor treatment and several immune tolerance induction attempts. Despite prior therapies, including recombinant Factor VIII and bypassing agents, the patient continued to experience severe bleeding episodes, leading to musculoskeletal complications and diminished quality of life. Transitioning to emicizumab, planned collaboratively with a specialized medical team, proved beneficial. Subcutaneous administration of emicizumab reduced treatment burden compared to previous therapies, leading to a significant reduction in bleeding episodes. Periodic quality of life assessments, including standardized questionnaires like SF-36 and EQ-5D, tracked improvements in treatment adherence, psychological well-being, and family relationships. Over the treatment period, bleeding episodes decreased significantly, with observed improvements in joint health. SF-36 and EQ-5D scores revealed challenges in movement-related functions and emotional well-being initially, but subsequent administrations showed improvements in health perception and slight enhancements in self-care and anxiety levels. The case underscores the efficacy of emicizumab in managing severe hemophilia A, particularly in patients with inhibitors unresponsive to conventional treatments. The multidisciplinary approach involving healthcare professionals ensured comprehensive support during treatment transition and long-term monitoring, highlighting the importance of innovative therapies like emicizumab in severe hemophilia management.

PO066

DON'T JUDGE A BOOK FROM ITS COVER... PEG IN

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Background: Mild hemophilia A (HA) is a congenital bleeding disorder defined by FVIII levels >5% and usually characterized by a mild hemorrhagic phenotype (minor and posttraumatic bleeding). In recent years, recombinant FVIII concentrates with a prolonged half-life (EHL-rFVIII) have been approved for prophylaxis and on-demand treatment. The incidence of neutralizing anti-FVIII antibodies (inhibitors) is generally low, being estimated at 5-7% in patients with mild and moderate HA (MMHA). This phenomenon occurs later in life and is usually associated with a change in hemorrhagic phenotype.
Case Report: A 18-years-old patient with mild hemophilia A and a moderate haemorrhagic phenotype (muscle haematomas during sporting activity, not hemarthrosis) turned to our center to begin prophylaxis for competitive sport. Laboratory tests showed normal hemoglobin levels and leukocyte count with mild thrombocytopenia (116,000/mm3), normal renal and hepatic function, and metabolic parameters. At coagulative tests: PT 93%, PTT 55", Fibrinogen 371 mg/dl, FVIII 11%, VWF:Ricof 120%. Citrate platelet count confirmed mild thrombocytopenia, autoimmune causes, viral infections, splenomegaly were excluded, the balance of vitamins and iron was normal. Stool antigen test for Helicobacter pylori resulted positive. Antibiotic therapy with amoxicillin+clavulanate, metronidazole and clarithromycin managed to eradicate the infection and the platelet count returned to within limits. At this point, prophylactic therapy was started with Turocotocg alfa PEGol 40IU/kg once a week and pharmacokinetics were scheduled after four weeks. Three weeks later, the patient played a volleyball match the day after infusion, and reported an ankle injury with pain, swelling and limitation of movement. The X-Ray was negative while the ultrasonography revealed hemarthrosis and impairment of the talofibular ligament. He continued to be treated with EHL-rFVIII without any benefit on pain. Therefore, we performed the factor VIII test with a level equal to 10% at 48 hours after treatment. Recovery FVIII post infusion was performed, revealing an inadequate level of FVIII at 29%. The APTT Mixing study corrected the coagulation profile and FVIII inhibitor was not detected. In the suspicion of anti-PEG inhibitor, we administered a SHL-rFVIII, obtaining a normal recovery at 95%. Anti-PEG antibody assay with ELISA test was positive, meanwhile the patients started a SHL-rFVIII treatment with a net clinical benefit and resolution of bleeding.
Conclusions: Anti-PEG antibodies can be found in healthy individuals as well as in patients who have not received PEGylated biotherapeutic drugs, especially in young adults. The immunogenic mechanism may be T-cell dependent, with or without neutralizing action on FVIII activity. We do not know whether the patient had anti-PEG antibodies before the first dose of PEGylated or whether there is an immunological correlation with the HP infection. As we know from the few cases described in the literature, anti-PEG antibodies could be associated with only a temporary reduction in FVIII recovery and generally disappear after continuous administration. However, with the ongoing hemarthrosis we considered it more appropriate to replace the drug with non-PEGylated rFVIII, to ensure adequate hemostasis. This case highlights the importance of administering a test dose and monitoring FVIII when changing FVIII concentrate to provide the patient with optimal treatment.

PO067

ACQUIRED HEMOPHILIA A AND BULLOUS PEMPHIGOID AS PARANEOPLASTIC MANIFESTATIONS OF LOW-GRADE UROTHELIAL CARCINOMA: A CASE REPORT

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Background: Acquired hemophilia A is a rare disease resulting from autoantibodies against endogenous factor VIII. Bullous pemphigoid is an autoimmune bullous disease. Both diseases may present as manifestations of cancer.
Case Report: A 61-year-old male patient diagnosed with bullous pemphigoid was started on oral methylprednisolone. A few weeks later, the patient presented to the emergency department with a gastrocnemius intramuscular hematoma. Blood tests showed severe anemia and prolonged activated partial thromboplastin time (aPTT). A mixing test was performed, with no correction of aPTT. Factor VIII was undetectable, with the presence of high levels of inhibitors on the Bethesda assay. Suspecting a paraneoplastic syndrome, computed tomography was performed, which revealed a bladder polyp. High-dose oral prednisone (1 mg/kg) was started, and polyp resection was postponed due to a high bleeding risk. Later, the patient also presented with a deltoid intramuscular hematoma, prompting the initiation of recombinant factor VIII and immunosuppressive therapy with rituximab. Six months later, aPTT and factor VIII levels normalized and the patient was able to undergo transurethral bladder resection. Histologic examination showed low-grade urothelial carcinoma. The cortisone therapy was discontinued 10 months after its initiation.
Conclusions: Acquired hemophilia A typically manifests as spontaneous and severe bleeding. Treatment involves controlling the source of bleeding and eradicating the factor VIII inhibitor. Investigating the underlying condition is mandatory as it may represent a manifestation of cancer, especially when associated with another paraneoplastic syndrome, such as bullous pemphigoid.

PO068

PROCOAGULANT ACTIVITY OF PHOSPHOLIPIDS, BUT NOT EXTRACELLULAR VESICLES-ASSOCIATED TISSUE FACTOR-DEPENDENT PROCOAGULANT ACTIVITY, IS CORRELATED WITH THROMBIN GENERATION PARAMETERS: PRELIMINARY RESULTS FROM AN ANGIOGRAPHICALLY-CONTROLLED STUDY

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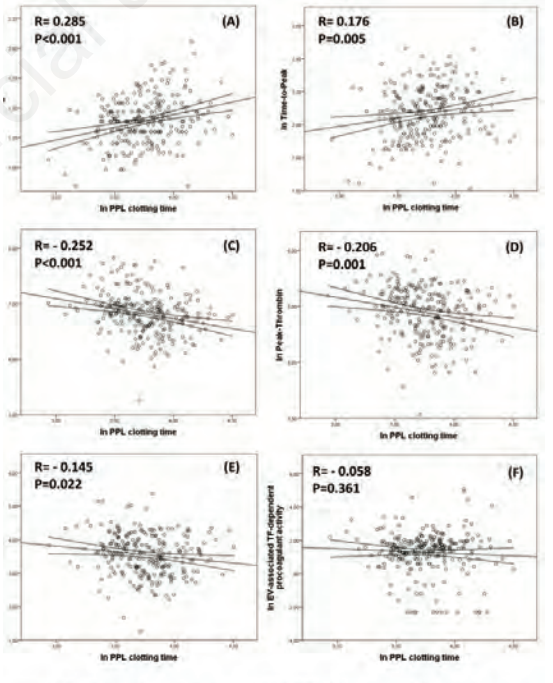
Background and Aims: Although coagulation plays a crucial role in the pathophysiology of atherothrombosis, the clinical significance of many coagulation biomarkers in ischemic heart disease (IHD) remains controversial so far. We aimed to assess some global coagulation biomarkers in a single-center, angiographically-controlled, cohort of subjects with or without coronary artery disease (CAD).
Methods: Procoagulant phospholipids (PPL) clotting time, extracellular vesicles-associated tissue factor-dependent (EV-TF) procoagulant activity, and thrombin generation (TG) were assessed in clinically stable subjects undergoing elective coronary angiography.
Results: Data on coagulation biomarkers were available for 297 subjects (males 71.7%; mean age 68.5±9.9 years): 54 subjects had normal coronary arteries (CAD-free group), 50 subjects had coronary lesions with stenosis <50% (CAD-borderline group), and 193 subjects had coronary lesions with stenosis ≥50% (CAD group). Fifty-two subjects had a history of previous myocardial infarction (MI). Forty-eight subjects taking oral anticoagulant therapies were excluded from further analysis.
There was a strong correlation between PPL clotting time and TG parameters, directly with lag-time and time-to-peak, inversely with endogenous thrombin potential (ETP), peak-thrombin, and mean rate index (MRI), while no correlation was found between EV-TF procoagulant activity and TG parameters, as well as between PPL clotting time and EV-TF procoagulant activity (Figure 1).



Correlations of procoagulant phospholipids (PPL) clotting time with thrombin generation parameters, i.e. Lag-Time (A), Time-to-Peak (B), Endogenous Thrombin Potential (C), Peak-Thrombin (D), and Mean Rate Index (E), and extracellular vesicles-associated tissue factor-dependent (EV-TF) procoagulant activity (F) in the study population after excluding subjects taking oral anticoagulant therapies (n=249).

Figure 1.

The association of PPL clotting time with lag-time (beta-coefficient 0.282, P<0.001), time-to-peak (beta-coefficient 0.152, P=0.018), ETP (beta-coefficient -0.238, P<0.001), and peak-thrombin (beta-coefficient -0.174,

P=0.006) were confirmed after adjustment for sex, age, CAD diagnosis, body mass index, creatinine, PT and aPTT levels. In a preliminary (but underpowered) case-control analysis, neither PPL clotting time, nor EV-TF procoagulant activity were associated with CAD, CAD severity or history of previous MI, while lag time was longer in patients with CAD and MI.
Conclusions: In this pilot study PPL clotting time, but not EV-associated TF-dependent procoagulant activity, correlated with TG parameters in subjects within an angiographically-controlled CAD cohort.

PO069

CHARACTERIZATION OF THE PLEIOTROPIC EFFECTS OF INCLISIRAN

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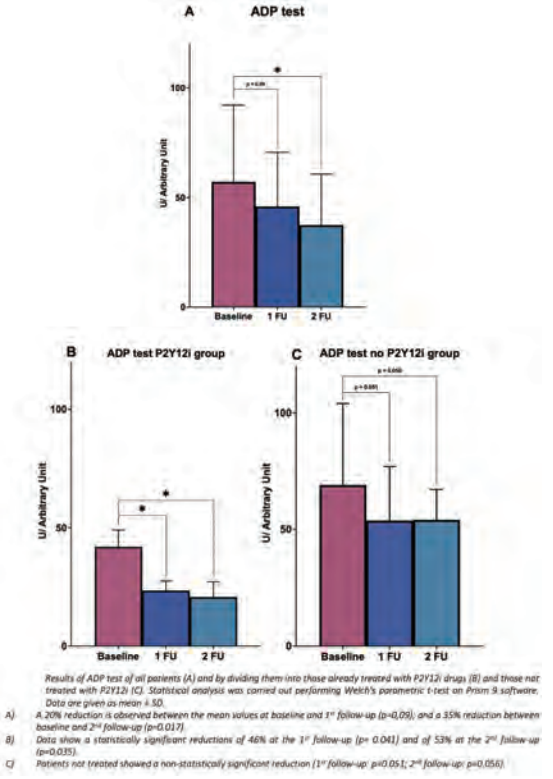
Background and Aims: Inclisiran, a small-interfering RNA (siRNA) that penetrates hepatocytes and blocks the translation of proprotein convertase subtilisin/kexin type 9 (PCSK9), represents a novel therapeutic approach with a convenient and infrequent dosing schedule to robustly lower low-density lipoprotein cholesterol (LDL-C). PCSK9 has been suggested to promote proinflammatory and prothrombotic effects beyond LDL-C regulation.
We therefore aimed to explore possible pleiotropic effects of this drug.
Methods: Consecutive patients who were deemed candidate for Inclisiran therapy according to ESC guidelines and Italian reimbursement criteria were enrolled in a prospective registry. Peripheral venous blood samples were collected before the first drug administration and after 3 and 9 months. Blood samples were tested for platelet activity performing ADP, ASPI, and TRAP tests on the semi-automated Multiplate Analyzer. Besides, erythrocyte aggregation and deformability were determined on fresh blood using a laser-assisted optical rotational cell analyzer (LORRCA, Mechatronics, Instruments, The Netherlands).
Results: Among the 53 study participants, 37 (21 males, mean age 59 years) underwent at least one follow-up blood sample; 25 of them started Inclisiran therapy for secondary prevention, the other 12 for primary prevention. No patient started therapy with P2Y12i drugs after the first administration of Inclisiran. Platelet reactivity according to ADP test was significantly reduced at follow-up (baseline 57 AU; 1st follow-up 46 AU, p=0,09; 2nd follow-up 37 AU, p=0.017), Figure 1A. Analyzing the results of the ADP test by dividing the patients into the two cohorts, those already treated with P2Y12i drugs and those not treated with P2Y12i, statistically significant reductions of 46% at the 1st follow-up (p= 0.041) and of 53% at the 2nd follow-up (p=0.035) in patients on P2Y12i antiplatelet therapy (Figure 1B) and a reduction of 22% (1st follow-up: p=0.051; 2nd follow-up: p=0.056) in patients not treated (Figure 1C). In fact, average values in patients not treated with P2Y12i for ADP test at Multiplate move from 69 AU (baseline) to 54 AU at the 2nd follow-up (p=0.056), when in diagnostic practice the cut-off value to consider inhibited platelet activity is 46 AU. Patients on therapy with P2Y12i, however, despite already being pharmacologically inhibited (average baseline values of 42 AU), show a further push towards platelet inhibition, reporting average values of 20 AU at the 2nd follow-up (p=0.035). The analysis of erythrocyte aggregation was not affected by Inclisiran administration irrespective of back-ground lipid lowering therapy: patients on statin therapy (AI: 66.8 *vs* 65.9; p=0.78), patients not receiving statin therapy (AI: 65 *vs* 64.7; p=0.89). Similarly, Inclisiran administration did not show to affect erythrocyte deformability, neither in patients on statin therapy (EI: 0.38 *vs* 0.39; p= 0.21) nor in those without back-ground lipid lowering therapy (EI: 0.41 *vs* 0.38; p= 0.06).
Conclusions: Although preliminary, our data suggest that Inclisiran appears capable of reducing platelet activity and inhibiting platelet activation via the P2Y12 receptor, regardless of the presence or absence of background antiplatelet therapy. Further studies and the enlargement of the patient sample of our ongoing study may consolidate these results and increase our knowledge about the possible pleiotropic effects of this drug.



Results of ADP test of all patients (A) and by dividing them into those already treated with P2Y12i drugs (B) and those not treated with P2Y12i (C). Statistical analysis was carried out performing Welch's parametric t-test on Prism 9 software. Data are given as mean ± SD.
A) A 20% reduction is observed between the mean values at baseline and 1st follow-up (p=0,09), and a 35% reduction between baseline and 2nd follow-up (p=0.017).
B) Data show a statistically significant reductions of 46% at the 1st follow-up (p= 0.041) and of 53% at the 2nd follow-up (p=0.035).
C) Patients not treated showed a non-statistically significant reduction (1st follow-up: p=0.051; 2nd follow-up: p=0.056).

Figure 1.

PO070

IMPACT OF ENDOVASCULAR TREATMENT ON IN-HOSPITAL FUNCTIONAL OUTCOMES IN ISCHEMIC STROKE IN THE REAL-LIFE: A RETROSPECTIVE STUDY

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Background and Aims: Stroke remains a leading cause of disability worldwide. Intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) are recommended treatments for acute ischemic stroke (AIS). However, the predictors of functional recovery following EVT±IVT have not been clearly identified. We aimed to investigate the impact of EVT±IVT, on functional outcome in patients with AIS.
Methods: A retrospective registry of 101 patients who underwent reperfusion treatments for AIS was analyzed to identify the prognostic factors of an unfavorable outcome, defined as a modified Ranking scale (mRS) ≥3 points at discharge. Logistic regression was performed for univariate and multivariate analyses to determine the association with unfavorable outcomes.
Results: Unfavorable outcomes at discharge occurred in 85 patients (84.1%). In the univariate analysis, predictors of unfavorable outcome included National Institutes of Health Stroke Scale (NIHSS) at presentation (odds ratio (OR) 1.19, 95% confidence interval (CI) 1.02-1.42, p=0.034), systemic arterial hypertension (SAH) (OR 3.42, 95% CI 1.12-10.53, p=0.029), general anesthesia procedure (OR 5.07, 95% CI 1.62-16.15, p=0.0051) and number of thromboaspiration attempts (OR 2.61, 95% CI 1.21-7.34, p=0.0343). In the multivariate model, SAH (OR 5.45, 95% CI 1.27-28.95, p=0.030), and modified treatment in cerebral infarction (mTICI) scores (OR 0.21, 95% CI 0.03-0.59, p=0.024) were independent predictors of unfavorable functional outcome.
Conclusions: In our retrospective study, SAH and ineffective cerebral reperfusion were independent predictors of unfavorable outcomes in patients treated with EVT±IVT. These findings emphasize the importance of rapid comprehensive patient assessment and effective endovascular treatment to optimize AIS functional outcome.

PO071

CARDIOVASCULAR RISK IN PATIENTS WITH POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA: FOCUS ON THE POTENTIAL ROLE OF LIPOPROTEIN(A)

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Background and Aims: Cardiovascular disease represents the main cause of mortality in Polycythemia Vera (PV) and Essential Thrombocythemia (TE) pts. The objectives of this study are to assess the potential role of cardiovascular (CV) risk factors, including LDL cholesterol (LDL-C) and Lipoprotein(a) [Lp(a)], in thrombotic events; to evaluate if altered levels of Lp(a) may modify CV risk stratification according to the European Society of Cardiology (ESC) and to compare ESC CV stratification with prognostic stratifications in use.
Methods: We analyzed 48 pts (16 PV and 32 TE), assessing hematologic parameters and ESC CV risk, including LDL-C and Lp(a). Lp(a) targets followed the Italian Atherosclerosis Society consensus (pathological >125 nmol/L, intermediate 75-125 nmol/L).
Results: Lp(a) values above 75 nmol/L were present in 6.25% of pts with PV and 3.1% of pts with moderate ESC CV risk. Thrombotic events occurred in 8 PV pts (75% venous) and 14 TE pts (79% arterial). Among pts with thrombotic events, Lp(a) levels were >75 nmol/L in 1 PV pt with acute coronary syndrome (ACS), in 1 TE pt with ACS, in 1 TE pt with 3 coronary artery diseases, in 1 TE pt with peripheral arterial disease (PAD), in 1 TE pt with stroke, and in 1 TE pt with PAD and deep vein thrombosis. In PV and TE pts, arterial hypertension was present in 66% and 37% of cases, diabetes mellitus in 6.25% and 12.1%, dyslipidemia in 75% and 87.5% and smoking habit in 25% and 15.6%, respectively. In pts cohorts with PV and TE, 78.6% and 40.6% of pts, respectively, had more than one risk factor, and within these two subgroups, 100% and 93% of the recorded thrombotic events occurred, respectively. 31% and 15.6% of PV and TE pts had LDL-C values at therapeutic goal. There was incongruity between hematologic prognostic stratification and ESC CV stratification in the case of 1 low-risk PV pt with moderate ESC risk with Lp(a) 136 nmol/L and 2 pts respectively low and intermediate r-IPSET-t risk with high ESC risk with Lp(a) values of 123 nmol/L and 215 nmol/L.
Conclusions: Classic CV risk factors, though common and associated with thrombotic events, are inadequately identified and managed. Prognostic scores should be integrated with ESC cardiovascular risk stratification to predict thrombotic risk more accurately. Lp(a) testing should be considered as a baseline screening due to its correlation with increased CV risk, potentially impacting ESC risk classification and expected mortality.

PO072

PREVALENCE OF USE OF LIPID-LOWERING TREATMENT AMONG ATRIAL FIBRILLATION PATIENTS ENROLLED IN THE START-AF REGISTER

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Background and Aim: Statin therapy is a cornerstone in the management of dyslipidemia, both in primary and secondary prevention of cardiovascular events. The survey on anticoagulated patients register (START-Register) is an italian independent, prospective, inception-cohort observational study aimed at providing information on patients treated with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).
Methods: In this study, we describe the cohort of atrial fibrillation (AF) patients enrolled in the START-Register reporting also outcomes and changes in anticoagulant prescription from 2011 to 2021. The study included 11,078 AF patients, enrolled in 47 Italian centers distributed all over the Country; the median age was 77 years (range 18-99 years); 6,029 (54.3%) were men; 5,135(46.4%) were on VKAs, and 5,943 (53.6%) were on DOACs. Among DOAC users, 4,022 (67.7%) patients were naive to anticoagulation, and 2,562 (43.1%) patients were treated with a reduced dose. Lipid-lowering treatment was recorded in 3823 (39.3%) patients. Hypertension, diabetes mellitus, coronary artery diseases, peripheral artery diseases, TIA/stroke and heart failure (p=0.000) are more frequent in patients treated with statins. Atorvastatin is prescribed in 46.0% of cases; simvastatin is prescribed in 27.2% of cases, and Rosuvastatin in 13.5% of cases.
Conclusions: Patients on lipid-lowering treatment are more frequently affected by cardiovascular risk factors with respect to patients not treated with lipid-lowering drugs.

PO073

POST-THROMBOTIC SYNDROME AND ROLE OF CARDIOVASCULAR RISK SCORES: PRELIMINARY RESULTS

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Background and Aims: Post-thrombotic syndrome (PTS) refers to signs and symptoms of venous hypertension due to chronic obstruction of the deep venous system after deep vein thrombosis (DVT). Atherosclerosis of different arterial districts is a common finding in patients suffering from PTS. Venous thrombosis and atherosclerosis seem to be two sides of the same coin. The objective of this study is to evaluate the role of cardiovascular risk scores (Framingham score, Framingham 2008 score and SCORE2) in post-thrombotic syndrome (residual thrombus and clinical signs according to the Villalta score).
Methods: An observational study was conducted at "Fondazione Policlinico Universitario A. Gemelli IRCCS", inside the national observational prospective register START-POST VTE (promoted by Fondazione Arianna). Data from ambulatory adult patients admitted to the Angiology Unit were collected. Compression Ultrasound (CUS) was performed at 3 and 6 months in patients suffering from DVT and cardiovascular risk scores (Framingham score, Framingham 2008 and SCORE 2) were calculated through clinical and laboratory tools.
Results: A total of 84 patients (mean age 66 years; male 49%) were enrolled. Diagnosis
of PTS were made in 40.5% of patients. A relationship was observed between Framingham score 2008 and PTS, regardless of the severity estimated by the Villalta score. The relationship between SPT and SCORE2 and the relationship between SPT and Framingham score were not significant. Interestingly, the three cardiovascular risk scores differ only for the presence of diabetes, an item included only in the Framingham 2008.
Conclusions: The study highlights the importance of «venous pathology» in terms of cardiovascular disease, which for a long time, was considered more commonly related to arterial vascular disease alone. Moreover our results suggests the possible role of diabetes among the mechanisms underlying thrombotic events in venous and arterial systems as a factor determining damage to the microcirculation.

PO074

GENETIC CHARACTERIZATION OF THE KIV2 LPA POLYMORPHISM IN SUBJECTS WITH BICUSPID AORTIC VALVE: COMPARISON BETWEEN QPCR AND DDPCR METHODS

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Background and Aims: The bicuspid aortic valve (BAV) is a congenital cardiac malformation with an incidence ranging from 0.5 and 2.0% in the general population. Beyond hemodynamic valvular impairment, a frequent determinant of BAV natural history, dyslipidemia and elevated lipoprotein (a) [Lp(a)] levels also favor progression and complications of aortic valve

disease. Lp(a) levels are known to be under a strict genetic control (heritability of the trait >90%) and are largely influenced by LPA Kringle IV type 2 (KIV-2) size polymorphism affecting apolipoprotein (a) isoform dimensions. In the present study, we evaluated the relationship between LPA KIV-2 repeat number, measured through digital droplet PCR (ddPCR) beyond traditional quantitative real-time PCR method (qPCR), and Lp(a) levels with the complications of calcification and valve stenosis in patients affected by BAV.

Methods: The genetic characterization of the LPA KIV2 polymorphism was carried out through ddPCR (QX200 Droplet Digital PCR System) and qPCR [7900HT Fast Real-Time PCR System (Applied Biosystem). Lp(a) levels were assessed by immunotubidimetric assay (Randox).

Results: The cohort under analysis is represented by 64 subjects of Caucasian origin [79.7% male; median age 45.50 years [interquartile range (IQR): 29.50-52.75)] referred to the Center for Cardiovascular Diagnosis or Referral Center for Marfan syndrome or related disorders, AOU Careggi. As expected from literature, for both methods, an inverse correlation is observed between Lp(a) levels and the number of LPA KIV2 repeats, although statistical significance is not reached (ddPCR: R=-0.144, p =0.256; qPCR: R=-0.114, p=0.371). However, subgrouping the cohort according to Lp(a) 500 mg/L cut-off value, the ddPCR shows significantly lower values of repeats in the group of subjects with higher levels of Lp(a) [median (IQR) ddPCR 5.29 (4.84-5.60) *vs* 13.00 (9.23-24.45), p=0.005], while qPCR shows similar, but not significant, results [median (IQR) qPCR 13.00 (12.00-17.50) *vs* 18.00 (12.00-30.00), p=0.577]. As concerns KIV2 repeat evaluation according to BAV complications, in subjects with severe calcification, in whom significantly higher Lp(a) levels were reported (p=0.016), a more marked decrease in repeat values with ddPCR [median (IQR): severe calcification 5.86 (5.34-9.23) *vs* no calcification/mild-moderate calcification 13.00 (8.22-24.45), p=0.073] compared to qPCR [median (IQR) severe calcification 12.00 (12.00-12.5) *vs* no calcification/mild-moderate calcification 18, 00 (12.00-30.00), p=0.147] was found. The LPA KIV2 polymorphism was also investigated in BAV subjects according to the presence of stenosis and we observed a decreased, even if not statistically significant, number of repeats measured with both methodological approaches, ddPCR and qPCR, in subjects with stenosis, also reporting significantly higher Lp(a) levels (p=0.016), with respect to those without this complication [median (IQR): ddPCR 10.70 (6.01- 21.04) *vs* 13.11 (7.75- 24.48); qPCR 16.00 (12.00- 22.75) *vs* 18.00 (12.00- 30.00)].

Conclusions: Data obtained highlight a greater potential of the ddPCR approach *vs* qPCR in identifying subjects with bicuspid aortic valve complications, probably due to the greater stability and less variability in the identification of KIV2 repeats. Moreover, these results confirm and improve the data previously obtained with qPCR alone in relation to the role of LPA KIV2 polymorphism in complications associated with VAB.

PO075

CIRCULATING LIPOPROTEIN (A) LEVELS IN ATRIAL FIBRILLATION PATIENTS ENROLLED IN THE OBSERVATIONAL STRAT-AF STUDY

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Introduction: Atrial fibrillation (AF) is the most common supraventricular arrhythmia in clinical practice. Epidemiological and mendelian randomization studies provided strong support for a causal role of elevated Lp(a) in the development of atherosclerotic cardiovascular disease. Aim of the study was to evaluate the association between circulating levels of Lp(a) with the cerebral microangiopathy using MRI in a cohort of AF patients on oral anticoagulant therapy.

Methods: The Strat-AF study is an observational, prospective, single-center hospital-based study enrolling patients with atrial fibrillation, aged 65 years or older, referring to Center of Atherothrombotic Disease of our University Hospital (AOU Careggi) for the management of oral anticoagulation therapy. Recruited patients are evaluated by means of a comprehensive protocol, with clinical, cerebral magnetic resonance imaging and circulating biomarkers assessment. The main outcome is the evaluation of cerebral microangiopathy using MRI [lacunar infarcts, non-lacunar infarcts, microbleeds (CMB), hyperintensity of the white matter (WMH), enlarged perivascular spaces basal ganglia (bgEPVS) and SVDs (small vessel disease score)]. Lp(a), LDL- and HDL-cholesterol (LDL-C and HDL-C) were assessed by using commercial kits (Roche Diagnostics, Italy).

Results: We evaluated 142 patients for whom a complete evaluation of Lp(a), lipid profile and cerebral microangiopathy markers was available. In the Strat-AF population, we found higher, even if not statistically significant, levels of Lp(a) in patients with an history of stroke with respect to patients without [20.5 (11.8-73.8) nmol/L *vs.* 16.0 (6.0-43.0) nmol/L, p=0.060]. Concerning the distributions of neuroimaging characteristics: a moderate-to-severe degree of WMH was present in 66.2% (n=94), at least one lacunar infarct in 21.8% (n=31), at least one non-lacunar infarct in 33.8% (n=48), at least one CMB in 18.3% (n=26) and at least one sign of SVD in 55.5% (n=91). Patients with lacunar or non-lacunar Infarcts had similar Lp(a), HDL-C and LDL-C levels with respect of patients without. Comparing patients with or without a moderate-to-severe degree of WMH and patients with or

without bgEPVS, no significant differences of Lp(a), HDL-C ad LDL-C were detected. Furthermore, we did not find any significant difference between patients with and without CMBs in terms of Lp(a) and HDL-C, whereas LDL-C levels were significantly lower in patients with at least 1 CMB than in patients without CMBs (47.5±15.1 *vs.* 52.1±14.5 mg/dL, p=0.042). Patients with 3 or 4 signs of SVD had lower, but not statistically significant, levels of LDL-C than patient with ≤2 signs of SVD (48.9±16.8 mg/dL *vs.* 51.3±14.4 mg/dL). Percentage of patients with Lp(a)>125 nmol/L did not differ between patients with or without each of the cerebral microangiopathy markers. At multivariate analysis, adjusted for age, sex, CHA2DS2-VASc, HAS-BLED, statin treatment and dyslipidemia, there was a non-significant tendency towards the association between the lower levels of LDL-C and the presence of CMB [OR=0.62 (95% CI 0.36-1.07), p=0.085].
Conclusions: Lipoprotein(a), and HDL-C assessment in patients enrolled in the Strat-AF study did not demonstrate a significant association between the presence of cerebral microangiopathy with these biomarkers. Only a slight, but not significant, association between the presence of CMB and lower levels of LDL-C was found.

PO076

HIGHER LIPOPROTEIN (A) CIRCULATING LEVELS ARE ASSOCIATED WITH ENHANCED LIPID PEROXIDATION AND THROMBOXANE-DEPENDENT PLATELET ACTIVATION

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Background: Lipoprotein(a) [Lp(a)] is one of the strongest genetically determined risk factors for cardiovascular disease (CVD). The physiological function of Lp(a) is still in the dark. It is believed that Lp(a) has proatherogenic and prothrombotic properties. Analysis from the ASPREE trial revealed that the net clinical benefit of low-dose in primary prevention in the elderly is uncertain, but is largely magnified when considering participant who are carriers of the genetic variants associated with high lp(a) levels. A mendelian randomization analysis has suggested that lowering Lp(a) is associated with reduced cardiovascular risk, making it an attractive target for preventing cardiovascular events. Our main hypothesis is that the higher risk of atherothrombosis associated with higher Lp(a) levels may be mediated by increased lipid peroxidation and platelet activation.
Objectives: The primary aim of the study was to evaluate the extent of platelet activation and lipid peroxidation in subjects with higher *vs.* lower Lp(a) levels, independent of traditional CV risk factors.
Methods: In a case control study, we enrolled donors referring to the Blood Transfusion Service of Pescara Hospital with levels of Lp(a) above (n=20) or below (n=20) 50 mg/dL. Urine and fasting blood sampling were performed. Patients were evaluated for clinical assessment and urinary metabolites mirroring TX-dependent platelet activation (11-dehydro-TXB2) and lipid peroxidation (8-iso-PGF2α).
Results: Subjects with higher levels of Lp(a) were male (p=0.025), with higher levels of total cholesterol (p=0.026) and low-density lipoprotein cholesterol (p=0.020) levels. Participants with high Lp(a) tended to take more statins (n=0 *vs.* n=3, p=0.096) than patients with low Lp(a) The urinary excretion rate of the F2-isoprostane 8-iso-PGF2α (p=0.039) and of 11-dehydro-TXB2 (p=0.033), *in vivo* markers of lipid peroxidation and platelet activation, respectively, were higher in subjects with elevated Lp(a) levels. A direct correlation was found between urinary 8-iso-PGF2α and 11-dehydro-TXB2 in the entire group of subjects (rho=0.346, P<0.038) confirming also in this setting the well acknowledged cause and effect relationship between lipid peroxidation and platelet activation (Figure 1).
Conclusions: We showed that higher Lp(a) levels may affect lipid peroxidation, probably through ROS formation, and that 8-iso-PGF2alpha may elicit thromboxane-dependent platelet activation by acting as a partial agonist of the thromboxane receptor even in the presence of subthreshold concentrations of other agonists. This may explain the wider relative risk reduction observed with low dose aspirin in carriers of the genotype associated with higher Lp (a) levels, as compared with comparable populations without this genetic risk factor. Further studies are needed to ascertain whether Lp(a) also exerts a direct role on platelet activation.

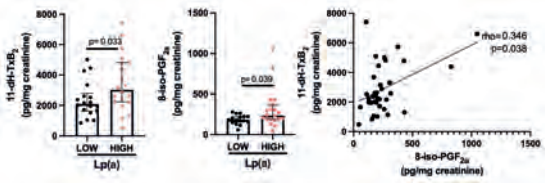

Figure 1.

PO077

CHARACTERIZATION OF THE EFFECT OF THE VASCULAR DOSAGE (2,5 MG BID) OF RIVAROXABAN ON CLOTTING ACTIVATION AND PLATELET FUNCTION

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Background and Aims: The addition of Rivaroxaban 2.5 mg BID to antiplatelet therapy with acetylsalicylic acid (ASA) has been proven to be an effective alternative to antiplatelet therapy alone for the secondary prevention of vascular events in patients with symptomatic peripheral arterial disease (PAD), as demonstrated by the multicentric and international COMPASS study. The rationale for using Rivaroxaban in secondary prevention in these patients is its direct inhibition of factor Xa and consequent reduction of thrombin levels, a known inducer of platelet function. However, the drug's impact on platelet function itself has not been fully elucidated, with very limited data available on its antiplatelet activity.
Methods: Our study recruited patients referred to the SOD Atherothrombotic Diseases of Careggi Hospital diagnosed with symptomatic PAD of the lower limb who were prescribed Rivaroxaban 2.5 mg BID in addition to ASA for bypass surgery, PCA revascularization of the lower limb, prior limb or foot amputation due to arterial vascular disease, or clinical diagnosis of intermittent claudication, associated with one or more of the following conditions: (i) ankle/arm blood pressure ratio <0.90, (ii) peripheral arterial stenosis ≥50% documented with angiography or arterial Doppler echo, or (iii) revascularized or asymptomatic carotid stenosis ≥50%. Venous blood samples were taken before starting Rivaroxaban 2.5 mg BID therapy (T0) and at least one month after initiation of the therapy (T1). We analyzed the effect of the Rivaroxaban and ASA combination on the parameters of the thrombin generation curve, on platelet function by evaluating ARU (Aspirin Reaction Unit) and PRU (P2Y12 Reaction Unit) and on two hemorheological parameters (erythrocyte deformability and erythrocyte aggregability).
Results: Our population consisted of 25 patients, 7 (28%) women, with a mean age of 70.3±7.1 years. Eight (32%) patients had undergone bypass surgery, 10 (40%) had a PCA revascularization, 4 (16%) had combined surgery, and 3 (12%) had a clinical diagnosis of intermittent claudication. Comparing the values obtained at time T0 and T1, we found alterations in almost all kinetic parameters of the thrombin generation curve (Lag time T0 3.93 *vs* T1 4.52, p=0.05; Peak T0 211.85 *vs* T1 173, p=0.04; ttPeak T0 7.14 *vs* T1 9.14, p=0.016). No differences in the other analyzed parameters were detected (ARU T0 492.1 *vs* T1 468.9, p=0.904; erythrocyte aggregability T0 67.3 *vs* T1 67.8, p=0.497; deformability T0 0.393 *vs* T1 0.397, p=0.375). The only statistically significant difference was found for PRU (P2Y12 Reaction Units), which reflects the response to antiplatelet therapy with P2Y12 receptor inhibitors (T0 159.6 *vs* T1 229.2, p=0.011) but this result is due to the discontinuation of dual antiplatelet therapy in 24 patients (96%) of our cohort.
Conclusions: Our study demonstrates an inhibition of thrombin generation with Rivaroxaban 2.5 mg BID without a direct and quantifiable effect on the parameters related to platelet aggregation induced by AA and P2Y12. Further studies are needed in order to establish a possible antiplatelet effect on platelet function induced by tissue factor.

PO078

THE ROLE OF INFLAMMATION, HAEMOSTASIS AND EXTRACELLULAR MATRIX IN PREDICTING THE APPEARANCE OF INSTRUMENTAL SIGNS OF CEREBRAL MICROANGIOPATHY IN ATRIAL FIBRILLATION PATIENTS ON ORAL ANTICOAGULANT THERAPY: INSIGHTS FROM THE STRAT-AF STUDY

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Introduction: In anticoagulated atrial fibrillation patients, the validity of models recommended for the stratification of the risk ratio between benefits and hemorrhage risk is limited. We hypothesize that biological markers – both circulating and neuroimaging-based – and their possible interaction, might improve the prediction of bleeding and thombotic risk in anticoagulated atrial fibrillation patients.
Methods: The Strat-AF study is an observational, prospective, single-center hospital-based study enrolling patients with atrial fibrillation, aged 65 years or older, and with no contraindications to undergo magnetic resonance imaging, referring to Center of Atherothrombotic Disease of our University Hospital (AOU Careggi) for the management of oral anticoagulation therapy. Recruited patients are evaluated by means of a comprehensive protocol, with clinical, cerebral magnetic resonance imaging and circulating biomarkers assessment. One of the main outcomes is the evaluation of the role of circulating biomarkers of inflammation (IL-6, IL-8, TNFα, IL-4, IL-10, CCL2, CXCL10, ICAM-1, VCAM-1, VEGF), haemostasis (PAI-1, CLT, vWF) and extracellular matrix remodeling (MMP-2, -7, -8, -9, -12, TIMP-1, -2, -3, -4) in predicting the appareance of new signs of cerebral microangiopathy using MRI at a 18-months follow-up [lacunar infarcts, non-lacunar infarcts, cerebral microbleeds (CMB), hyperintensity of the white matter (WMH), basal ganglia enlarged peri-vascular spaces (bgEPVS), SVDs (small vessel disease score)] in AF patients on oral anticoagulant therapy. Starting from September 2017, 170 patients (mean age 77.7±6.8, range 65-97; 34.7% females) were enrolled. Concerning the type of oral anticoagulant, 52 patients (30.6%) were on vitamin K antagonists, and 118 (69.4%) were on direct oral anticoagulants.
Results: On multivariate analysis, adjusted for age, sex, CHA2DS2-VASc, HAS-BLED and type of anticoagu-

lant, independent predictors were: high levels of IL-8 (Interleukin-8) and of TIMP-4 (Tissue Inhibitors of Metalloproteinases-9) for the appearance of new lacunar infarcts [OR=1.69 (95% C.I. 1.04-2.74), p=0.036 and OR=1.80 (95% C.I. 1.10-2.95), p=0.020, respectively].
Conclusions: The Strat-AF study may be an essential step towards the exploration of the role of a combined clinical biomarker or multiple biomarker models in predicting the onset of new instrumental signs of cerebral microangiopathy in patient with atrial fibrillation. Our results might sustain the incorporation of such new markers in the existing stroke prediction schemes by the demonstration of a greater incremental value in predicting stroke risk and improvement in clinical outcomes in a cost-effective fashion.

PO079

THE ROLE OF INFLAMMATION, HAEMOSTASIS AND EXTRACELLULAR MATRIX IN THE STRATIFICATION OF MOTOR AND COGNITIVE PERFORMANCE OF PATIENTS WITH ATRIAL FIBRILLATION ON ORAL ANTICOAGULANT THERAPY: THE STRAT-AF STUDY

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Background: Atrial fibrillation (AF) is the most common supraventricular arrhythmia in clinical practice. The relationship between AF and cognitive and motor impairment is likely to be multifactorial and more data are needed to fill the knowledge gap concerning the underlying pathogenic mechanisms. We hypothesize that biomarkers of inflammation (IL-6, IL-8, TNFα, IL-4, IL-10, CCL2, CXCL10, ICAM-1, VCAM-1, VEGF), haemostasis (PAI-1, CLT, vWF) and extracellular matrix remodeling (MMP-2, -7, -8, -9, -12, TIMP-1, -2, -3, -4) might play a role in the stratification of motor and cognitive performance in anticoagulated AF patients.
Methods: The Strat-AF study is an observational, prospective, single-center hospital-based study enrolling patients with atrial fibrillation, aged 65 years or older, and with no contraindications to undergo magnetic resonance imaging, referring to Center of Atherothrombotic Disease of our University Hospital (AOU Careggi) for the management of oral anticoagulation therapy. Recruited patients are evaluated by means of a wide neuropsychological battery [Montreal Cognitive Assessment (MoCA) test, Rey Auditory-Verbal Learning immediate and delayed recall, short story recall, Stroop test, semantic verbal fluency test and sentence construction test]. Functional status was evaluated by means of Basic Activities of Daily Living scale (BADL) and Instrumental Activities of Daily Living scale (IADL). Motor performance was evaluated by means of the Short Physical Performance Battery (SPPB). Starting from September 2017, 170 patients [mean age 77.7.±6.8, n=59 (34.7%) females] were enrolled. Concerning the type of oral anticoagulant, 52 patients (30.6%) were on VKA, and 118 (69.4%) were on DOACs.
Results: Concerning the cognitive performance, the circulating levels of IL-10 were significantly associated with a worse performance both in MoCA test and in Stroop test (rho=-0.161, p=0.031 and rho=-0.178 and p=0.022, respectively), whereas the circulating levels of VCAM-1 and vWF were significantly associated with a worse performance in Stroop test (rho=-0.241, p=0.002 and rho=-0.235, p=0.001, respectively). Taking into account the motor performance using the SPPB, the circulating levels of PAI-1 and vWF were significantly associated with a worse motor performance (rho=-0.339, p<0.001 and rho=-0.171, p=0.026, respectively). If we dichotomize the patients according to the score obtained at the SPPB, in particular with regard to the normality cut-off (SSPB ≥10 points), both PAI-1 and vWF circulating levels were significantly higher in patients with a reduced score on the SPPB compared to patients with a normal score [10.75 (7.58-17.36) *vs.* 7.99 (6.37-10.58), p<0.001 and 191.00 (137.40-217.80) *vs.* 146.80 (118.60-199.60), p=0.012, respectively].
Conclusions: Our results suggest a possible role of inflammation and haemostasis in reducing motor and cognitive performance in atrial fibrillation patients on oral anticoagulant therapy. It is known that alterations of the hemostatic system are correlated with the presence and progression of the cerebral small vessel disease which - in turn - is associated both with the worsening of the motor performance of the lower limbs and with cognitive impairment. Our results are intended to be «hypothesis generators». Further studies are certainly necessary to evaluate the clinical importance of such biomarkers in the global functional stratification of patients suffering from AF.

PO080

PROLONGED ACTIVATED PARTIAL THROMBOPLASTIN TIME OF UNKNOWN ETIOLOGY: A SYSTEMATIC EVALUATION OF CAUSES

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Background: A prolonged activated partial thrombo-

plastin time (APTT) is one of the most frequent reasons why outpatients are referred for hemostasis consultation. Nevertheless, very few data are available on the relative contribution of individual causes of this common clinical scenario. Here, we present a systematic evaluation of all causes of APTT prolongation in a consecutive population of outpatients referred for specialized hemostasis consultation during a 25-year period (from 1997 to 2022).

Aims: The study was designed as a retrospective cohort study performed in the outpatient hemostasis clinic of Hemostasis Centre of AORN S. Moscati (AV, Italy). The aim of providing data on the relative contribution of different conditions for APTT prolongations.

Methods: Datas were obtained from the tests done in the laboratory of the Hemostasis Centre. All assays were performed in hemostasis laboratory with in automated coagulometers (Siemens XP Healthcare, Munich, Germany; ACL TOP-500, Werfen, Madrid, Spain). For the APTT, the following reagents were used during the study period: Actin FSL (Siemens Healthcare) from 1997 to 2010, and HemosIL APTT-SP (Werfen) from 2010 to 2022.

Results: Among 732 consecutive patients, the most frequent causes were antiphospholipid antibodies in 51.50%, coagulation factor deficiencies in 33.90%, and vitamin K deficiency/liver disease in 5.90%. Consumption coagulopathy in 3.60%; interference from drugs in 2.83%, inhibitor deficiency in 1.55%; Hemophilia A in 0.71%. A definite cause was not identified in 0.01% of patients (Figure 1).

Conclusions: A specific diagnosis for the prolonged APTT was defined in 99.9% of patients. In conclusions, our study provides contemporary data on the relative distribution of the causes for APTT prolongation in one of the most common clinical scenarios of consultative hemostasis, confirming the antiphospholipid antibodies as the main cause of this laboratory alteration, and highlighting the significance of a prolonged APTT in absence of a specific disease of hemostasis.

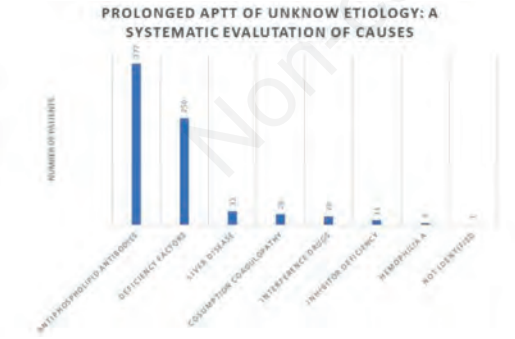

Figure 1.

PO081

DIRECT ORAL ANTICOAGULANT IN LABORATORY PRACTICE: HOW THEIR STABILITY RESPONDS UNDER DIFFERENT STORAGE CONDITIONS OF BLOOD SAMPLES

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Background and Aims: Since DOACs have an efficiency comparable to that of vitamin K antagonists with safer drug profiles and a most broad therapeutic window, they have widely replaced them in many indications. However, there are clinical conditions in which laboratory measurement of DOACs should be performed. Therefore, specific quantitative methods (dabigatran coagulometric assay and anti-Xa chromogenic assay with FXa inhibitor drug-specific calibrators) should only be used for determination of DOACs concentration. The aim of the study was to evaluate the *in vitro* stability of DOACs, using functional coagulation assays, in blood samples of 182 patients under different storage conditions.

Methods: All assays were performed on a fully automated coagulation analyzer of the ACL Top family as per manufacturers' instructions. The analyte concentration was determined immediately after blood collection (baseline); after storage of citrated whole blood (PL WB) at room temperature and citrated plasma at room temperature, at 4°C and -20°C (PL RT; PL 4°C; PL -20°C) for 24h, respectively.

Results: Among the 182 study participants, 46 were taking apixaban (17 men and 29 women), 42 were taking rivaroxaban (29 men and 13 women), 48 were taking edoxaban (22 men and 26 women) and 46 were taking dabigatran (24 men and 22 women) for both venous thromboembolism or atrial fibrillation. Data are given as median (75th and 25th percentiles) of apixaban, rivaroxaban, edoxaban and dabigatran and were 90 ng/mL (45-157), 58 ng/mL (24-113), 49 ng/mL (34-77) and 56 ng/mL (40-126), respectively. The medians of relative recovery after 24h (of all storage conditions: PL WB; PL RT; PL 4°C; PL -20°C) were the 98-100% for apixaban, 95–97% for rivaroxaban, 93–96% for edoxaban and 100–102% for dabigatran, of the baseline values (Table 1). The acceptable change limit (ACL) has been defined for all four DOACs using the formula ACL%=±2.77 * CV MAX (Oddoze et al; 2012). The calculated ACLs were ±13.9% for apixaban, ±11.2% for rivaroxaban, ±16.9% for edoxaban and ±19.7% for dabigatran, respectively. The analyte stability of all DOACs using functional coagulation assays was preserved for 24h under all investigated storage conditions, as the highest mean percentage deviation reached between all four DOACs was 7% (edoxaban Plasma RT). Overall, there were no significant differences over time for the 4 measurements for any of the DOACs tested. Mann-Whitney nonparametric t-test were performed for every condition of all DOACs. To evaluate the systematic error introduced using different storage conditions and to establish whether these alternative storage methods are acceptable to be used, non-parametric Passing-Bablok regression analysis war performed and showed a non-significant deviation from linearity (p >0.05) for every condition of all DOACs,

demonstrating the absence of systematic error between the method in use (Baseline) and the different storage conditions tested.

Conclusions: Data show that all ACL Top assays for DOACs are stable and the correct determination of plasma concentrations can be reached even if either citrate whole blood or citrate plasma are stored for 24h prior to analysis. No systematic error occurs from the regression analysis, suggesting that alternative storage methods could be used in laboratory practice to monitoring therapy with DOACs. Further measurements could lead to a consolidation of these results to be used in clinical diagnostic practice.

Table 1.

Results for apixaban, rivaroxaban, edoxaban, dabigatran – showing absolute and relative values at specific time points (T_0 and after 24 hours) under different sample storage conditions.

Analyte	Baseline value	Sample type	After 24 h
Apixaban	90 ng/mL (45-157)	WB RT Plasma RT Plasma 4°C Plasma -20°C	96 ng/mL Ø (49-157) 91 ng/mL Ø (46-157) 91 ng/mL Ø (45-157) 89 ng/mL Ø (48-156)
Apixaban	100% (100-100)	WB RT Plasma RT Plasma 4°C Plasma -20°C	98% (94-102) 100% (96-102) 98% (94-101) 98% (92-100)
Rivaroxaban	58 ng/mL (24-113)	WB RT Plasma RT Plasma 4°C Plasma -20°C	57 ng/mL Ø (20-111) 50 ng/mL Ø (18-108) 48 ng/mL Ø (19-106) 49 ng/mL Ø (18-106)
Rivaroxaban	100% (100-100)	WB RT Plasma RT Plasma 4°C Plasma -20°C	95% (92-99) 97% (90-102) 96% (91-100) 95% (87-99)
Edoxaban	49 ng/mL (34-77)	WB RT Plasma RT Plasma 4°C Plasma -20°C	47 ng/mL Ø (30-87) 45 ng/mL Ø (29-73) 46 ng/mL Ø (29-68) 46 ng/mL Ø (28-75)
Edoxaban	100% (100-100)	WB RT Plasma RT Plasma 4°C Plasma -20°C	96% (88-100) 93% (88-97) 94% (87-99) 94% (84-99)
Dabigatran	56 ng/mL (40-126)	WB RT Plasma RT Plasma 4°C Plasma -20°C	62 ng/mL Ø (37-123) 56 ng/mL Ø (38-120) 62 ng/mL Ø (40-121) 60 ng/mL Ø (38-113)
Dabigatran	100% (100-100)	WB RT Plasma RT Plasma 4°C Plasma -20°C	100% (95-111) 102% (95-109) 101% (95-110) 101% (93-108)

Table shows baseline value and the respective difference of the other storage conditions (non parametric t-tests, calculated p-values are purely descriptive) Øp > 0.05. Data are given as median (75th and 25th percentiles). RT: Room temperature; WB: whole blood.

PO082

A HIDDEN CASE OF ACQUIRED HEMOPHILIA: DETECTION BY LABORATORY

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Background: Inhibitor coagulation factors are neutralizing antibody against coagulation factor preventing coagulation cascade. The most common inhibitor is the one against FVIII (acquired hemophilia), but there are others against different coagulation factors. FVIII's inhibitors can develop in two different ways: - as a consequence of the therapy for hereditary hemophilia, - in association with a clinical condition such as autoimmune diseases, solid and hematological tumors, drugs or pregnancy. Second case is the most difficult to demonstrate with laboratory tests; it is always associated with muscular and mucosal hematomas and aPTT prolongation, which was never observed before. Hematologists can confirm the presence of inhibitors by requesting mixing test. The mix corrects factors deficiency at first but not after two hours of incubation at 37°C, in fact FVIII's inhibitors are time and temperature dependent. Inhibitor quantification is based on Bethesda method: measure recovery clotting activity in a mixture containing an exogenous source of the factor and a plasma sample, which is gradually diluted before the test.

Case Report: P. L. (80 years old Caucasian female) went to ULSS2 Marca Trevigiana E.R. on 03/11/2023 by rheumatologist's advice, because of thrombocytopenia, anemia and high PCR value. Laboratory test confirmed anemia (80 g/L), thrombocytopenia (104.000 PLT/mL) and moderate PCR level (4,43 mg/dL); E.R. physician observed a lot of foot petechiae. Moreover, coagulation's screening tests revealed PT and aPTT prolongation (1,44 and 1,39 ratios, respectively). A few days after, P.L. was submitted to second level coagulation tests because aPTT prolongation was not cleared. We observed deficit of some intrinsic pathway (FVIII 10%, FIX 56%, FXI 102%, FXII 28%); Willebrand activity and antigen were normal and Lupus Anticoagulant research was negative. We performed inhibitor quantification by Bethesda method: we mixed 1:2 plasma sample with pool plasma; before the mixing test, we made serial dilutions of the plasma sample in order to mitigate the action of FVIII's antibodies. In fact, we find out which plasma dilution is requested to observe an FVIII recovery level between 25% and 75% (if recovery activity is >75% the inhibitor is absent). In this specific case we observed a maximum of 73% of FVIII recovery activity. Inhibitor calculation corresponded to 0,45 U.B. but this result underwent the method sensitivity (0,6 U.B), so it was reported as an absence of inhibitor. P. L. went to E.R. other times referring petechiae and hematomas each time. Second level coagulation test were reperformed: FVIII activity were worsened to 4,4%. Moreover, FVIII's inhibitor research discovered 5,3 U.B. In this case, we made plasma sample dilutions up to 1:5, in which we observed 48% of FVIII recovery activity. After one month of therapy, aPTT was normalized to 1,14 ratios but FVIII's inhibitor was estimated at 2,2 U.B. with 27,9% of FVIII level.

Conclusions: Coagulation is a complex balance between a lot of conditions; in fact, during the first inhibitor determination, Bethesda method sensitivity did not allow the antibody identification. Strong clinical suspicion led to test repetition after some time, detecting a low title of inhibitor but still with a high risk of spontaneous bleeding. Finally, therapy normalized aPTT and reduced bleeding risk but did not completely correct inhibitor activity.

PO083

THE ADDED VALUE OF THE SPECIALIST LABORATORY: A CASE OF APS

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Background: The Laboratory Medicine services play an essential role in patient care. They provide substantial information in many areas of the care process. The aim of this work is to demonstrate how, when communication is supported by solid expertise, it represents a fundamental pillar for the delivery of appropriate and safe care. In particular, in cases with a complex clinical picture like the one presented, the laboratory can become a guide and a reference for the correct diagnostic path.
Case Report: Here is the case of a 59-year-old woman who presented to the Emergency Department with abdominal colic and a history of Addison's disease and a previous episode of DVT. Laboratory tests were all normal except for aPTT test, which showed a significant increase (149 sec, 5.20 Ratio); this, in conjunction with abdominal pain, raised suspicion of acquired hemophilia. The sample was sent back to the laboratory for further tests. Thrombin time (TT) was first performed to rule out the presence of heparin, and a mixing test at zero time and after two hours of incubation at 37°C was conducted, showing no correction in either condition. The determination of factor VIII was then carried out, revealing a severe deficiency confirmed by the parallelism test (serial dilutions of the sample). While this seemed to support the initial clinical suspicion of acquired hemophilia, the lack of correction in the mixing test prompted hemostasis specialists to conduct further investigations. Other coagulation factors were then determined, all showing deficiencies. Further dilutions (up to 1:128) were performed in the parallelism test, which helped to exclude a factor deficiency and point towards a nonspecific interferent rather than an inhibitor of a single factor: the Lupus anticoagulant. The search for the Lupus anticoagulant was carried out in accordance with the latest guidelines and showed positivity in both tests performed (SCT and DRVVT). The positivity of the Anti β2-GP1 and Anticardiolipin antibodies further confirmed the laboratory criteria for antiphospholipid syndrome.
Conclusions: The case reported highlights the added value of hemostasis specialists, who, thanks to their practical and theoretical skills, have not stopped at mere numerical data but have deepened the diagnostic path of the patient, leading them towards a thrombotic rather than hemorrhagic pathology. Specifically, the second-level diagnostic investigation allowed to exclude the initial diagnostic hypothesis (acquired hemophilia) and to correlate the episodes of venous thromboembolism with antiphospholipid antibody syndrome, with comorbidity represented by Addison's disease.

PO084

COMPARISON OF THREE DIFFERENT METHODS TO STUDY THROMBIN GENERATION IN PATIENTS WITH LIVER CIRRHOSIS

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Background and Aims: Liver cirrhosis is characterized by both bleeding and thrombotic complications due to a rebalanced and potentially unstable hemostatic state. The thrombin generation (TG) assay, performed with the addition of thrombomodulin (TM), is a well-established tool for evaluating the coagulation process in cirrhosis. Cirrhotic patients have a normal to increased TG capacity in platelet-poor plasma (PPP) while whole blood (WB) TG may allow a more physiological assessment of coagulation thanks to the contribution of all circulating blood cells. The aim of this study is to understand how the TG profile in patients with liver cirrhosis changes by comparing three different TG assays.
Methods: Consecutive patients with liver cirrhosis of different severity were enrolled. Patients with previous or acute thrombosis and hepatocellular carcinoma were excluded. A group of healthy controls was also included. Three assays were performed within 4 hours from blood collection to assess TG. WB-TG was performed in freshly collected citrated whole blood by using trigger solutions containing 1pM tissue factor (TF) in the presence or absence of 20nM TM (microplate fluorometer [Fluoroskan AscentTM]). PPP-TG was performed by using trigger solutions containing 1pM TF with and w/o 1.5nM TM (Thrombinoscope BV). Finally, PPP-TG was also performed in an automated instrument (New Clot) using a trigger solution for intrinsic pathway (A) activation, containing 0.45pM TF and 200pM FIXa, and a trigger solution for extrinsic pathway (B) activation with 150pM TF and 40uM anti-FVIII C2-C5. All samples were measured in triplicate and the fluorogenic substrate Z-Gly-Gly-Arg AMC used for all the three methods.
Results: Ten healthy controls and 30 cirrhotic patients with different severity (Child-Pugh classification) were enrolled. When WB-TG and PPP-TG were performed without TM, the endogenous thrombin potential (ETP) was comparable between controls and patients in Child-Pugh stage A and B, while ETP was significantly lower in Child-Pugh C (Figure 1 A, C). In WB-TG with TM, the ETP was significantly higher in cirrhosis than controls in Child-Pugh A, comparable between patients and controls in Child-Pugh B, and reduced in Child-Pugh stage C (Figure 1 B). In PPP-TG with TM, cirrhotic patients had a significantly higher ETP than controls, independently of Child-Pugh stage (Figure 1 D). PPP-TG performed with the automated method showed that cirrhotic patients generate significantly less thrombin than healthy individuals with both trigger solutions A and B. Furthermore, there was a significant and progressive gradient of TG reduction from Child-Pugh stage A to C, with both trigger solutions A and B (Figure 1 E-H).
Conclusions: Different TG profiles in cirrhotic patients were identified depending on the method used. PPP-TG

indicated a significant hypercoagulable state, independently of cirrhosis severity, while WB-TG indicated a hypercoagulable state in less severe cirrhosis and a significant hypocoagulable state in severe cirrhosis. The third PPP-automated method showed a hypocoagulable state in cirrhosis worsening with the severity of liver dysfunction. In WB-TG and PPP-TG the quantity of thrombin generated is obtained indirectly from the TG curve (ETP), while the PPP-automated system directly provides the amount of thrombin generated after incubation with intrinsic and extrinsic pathways triggers, possibly providing a more physiological estimate of the thrombin capacity.

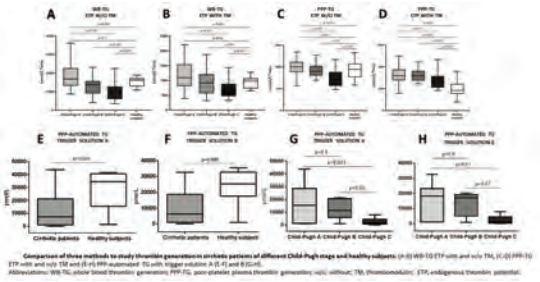

Figure 1.

PO085

USE OF THROMBIN GENERATION TEST IN THE MANAGEMENT OF HEMOPHILIC PATIENTS IN PROPHYLAXIS WITH EMICIZUMAB

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Background and Aims: Hemophilia A (HA) is a rare X-linked congenital hemorrhagic disease caused by the lack of coagulation factor VIII (FVIII). The gold standard therapy is prophylaxis with replacement treatment or with Emicizumab (Emz), a new non replacement drug. Literature data show that aPTT and FVIII assay, routinely used for monitoring replacement therapy, are not suitable for evaluating response to Emz and there are few real-world data on laboratory monitoring of this drug. In order to investigate hemostatic potential changes in patients (pts) treated with Emz, global coagulation assays, such as thrombin generation test (TGT), can be considered.

Methods: 6 pts, mean age 58 years, with severe HA without inhibitor who switched from replacement therapy to Emz were studied. After 4 loading doses, all pts received a maintenance dose of 1,5 mg/Kg weekly. Plasma samples were collected before treatment and during the follow up (FU). Following assays were performed: TGT with ST Genesia® (Stago, Asnieres-sur-Seine, France) using STG®-BleedScreen (STG-BLS), Emz plasmatic concentration and FVIII level. 2 most significant TGT parameters were evaluated, peak of thrombin generation (PEAK) and the endogenous thrombin potential (ETP). Clinical data were also collected: cardiovascular risk factors (*e.g.* obesity, smoke, hypertension, and prothrombotic coagulation defects), thrombotic or ischemic events, through level and annualized bleeding rate (ABR).

Results: In 4/6 (67%) pts an increase of thrombin generation (TG) was observed during Emz treatment, with values that reach normal ranges after switch (PEAK Height 121.3-201.1 nM: ETP 982-1680 nM.min). On the contrary the other 2/6 (33%) showed a significant decrease, one with FU values of PEAK and ETP respectively 65.92 nM and 795.4 nM.min and the other with values of 52.36 nM e 644 nM.min. Emz. plasmatic concentration during maintenance reached the expected values in 5/6 (40-66 µg/ml) but in one remained low (21.6 µg/ml). Clinical data analysis identified 2/6 pts with at least one cardiovascular risk factor, 1 pt with a previous thrombotic event, 1 pt positive for thrombophilic screening and the last two pts without any comorbidity. In 3 pts (50%) ABR score got to zero from higher values (respectively 11,2,12) while in 3 pts (50%) with previous 0 or 1 score, ABR remained the same. FVIII trough level before Emz ranged from 1% to 11,6% (Table 1).

Table 1.

Patient			Pz.1	Pz.2	Pz.3	Pz.4	Pz.5	Pz.6
Age			66	67	61	57	28	66
Cardiovascular risk factors			yes	no	no	no	no	yes
Thrombotic event			no	no	no	yes	no	no
Thrombofilic screening +			no	yes	no	no	no	no
FVIII trough level (%)			8	8	7	2,5	1	11,6
Emz. plasmatic concentration (µg/ml)	F.U.		39,5	54,8	50,9	66,1	49,1	21,6
TGT	Pre	Peak (nM)	77,1	34,86	110	119,9	92,6	92,19
		ETP (nM.min)	972,9	495,5	1053	1113	1164	1098
	F.U	Peak (nM)	110,5	116,7	65,92	175,5	87,78	52,36
		ETP (nM.min)	1285	1309	795,4	1204	1334	644
ABR	Pre		1	11	2	0	12	0
	Post		1	0	0	0	0	0

Conclusions: In agreement with the few data available in literature, the results highlight a high variability in TGT results. The increase in TGT parameters, compared to pre-treatment, in 4 pts (all with FVIII trough level ≤8%) agrees with the hypothetical increase in trough level considering FVIII's steady state around 10-15% with Emz. 2/6 pts showed a decrease in TGT parameters after switch. No correlation was found neither with prothrombotic and CV risk factors nor with ABR. However, one pt

has very low Emz concentration and the highest through level; the FU is still very short, but monitoring with TGT will help to understand if non-optimal levels of TG are sufficient to adequately protect even pts who required higher levels pre-treatment. Thrombin generation test (TGT) measures the hemostatic balance as a whole and it could support the clinician to define personalized treatment, monitoring pts case by case. However, results so far are elusive; it's necessary to have a larger casuistry to understand the best use of this laboratory monitoring.

PO086

COAGULATION PROFILES IN PATIENTS WITH WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS

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Background and Aims: Thromboembolic events are among the most important complications in patients suffering from wild-type transthyretin ATTR amyloidosis (ATTRwt), with a prevalence in the literature estimated between 6-28%. The high prevalence of atrial fibrillation (AF), mechanical cardiac atrial dysfunction and myopathy in ATTRwt patients appear to play an important role in the pathogenesis, though the etiology of thrombosis remains unclear. Thromboembolic events may also occur in patients with sinus rhythm and, albeit rarely, in adequately anticoagulated subjects as well. The suspicion is that the coagulation cascade might be involved, bearing in mind that the transthyretin molecule appears to contribute to the activation and regulation of the coagulation and fibrinolytic systems. The aim of the study was to evaluate whether it is possible to detect hyperactivation of the coagulation system using standard coagulation tests, viscoelastic tests and coagulation factors tests in patients with transthyretin amyloidosis.
Methods: Fourteen patients (median age 81.64 yrs; M/F 10/4) affected by ATTRwt in the absence of atrial fibrillation and not undergoing anticoagulant therapy were investigated. After obtaining written informed consent, a blood sample was collected by venipuncture directly into citrate tubes. Traditional coagulation tests, prothrombin time (PT)/international normalized ratio (INR), and partial thromboplastin (aPTT) were performed according to standard procedures. Coagulation factors FVIII, FX and FXI were measured using specific factor-deficient plasma. Antithrombin (AT) was measured using a thrombin-based chromogenic substrate assay; protein C (PC) and protein S were measured using commercial kits according to the manufacturer's instructions. Finally, antibodies such as lupus anticoagulant (LAC) , anticardiolipin (aCL), and anti-beta-2-glycoprotein 1 (anti-β2GP1) were also measured. Rotational Thromboelastometry (ROTEM) — a whole blood viscoelastic test — was performed according to standard protocols: INTEM (to assess intrinsic coagulation pathway), EXTEM (to assess the extrinsic coagulation pathway) and FIBTEM (to assess fibrinogen contribution to clot formation and stability) assays were used to measure the following parameters: i) clotting time (CT, sec), the time from the beginning of the coagulation analysis until an increase in amplitude of 2 mm; ii) clot formation time (CFT, sec), the time between an increase in amplitude of the thromboelastogram from 2 to 20 mm; iii) maximum clot firmness (MCF, mm), the maximum amplitude reached in the thromboelastogram; and alpha angle (α, degrees).
Results: All traditional coagulation times and coagulation factors were within the normal ranges. Tests for LAC, aCL and anti-β2GP1 antibodies were all negative. Similarly, all ROTEM® parameters were negative (Table 1).
Conclusions: Standard coagulation tests and viscoelastic tests did not allow to identify coagulation alterations in patients with transthyretin amyloidosis. Further investigations are needed to look into the hypothesis of hypercoagulability in this subset of patients.

Table 1.

SEX (male/female)	10/4	
MEDIAN AGE (years)	81,64	
	VALUE	REFERENCE RANGE
Prothrombin Time (%)	94,15 (± 17,29)	70 - 100
Activated Partial Thromboplastin Time (sec)	27,37 (± 2,74)	28,8 - 31
FVIII (%)	171,20 (± 79,53)	60 - 120
FXI (%)	113,01 (± 34,29)	80-120
FX (%)	83,45 (± 20,66)	80-120
Antithrombin (%)	86,49 (± 13,59)	80-120
Protein C coagulometric act (%)	98,50 (± 25)	80-120
Protein C chromogenic act (%)	112,25 (± 29,05)	70-130
Protein C ag (%)	112,21 (± 23,60)	80 - 120
Protein S coagulometric act (%)	112,81 (± 22,40)	70-130
Protein S free ag (%)	102,57 (± 15,73)	80 - 120
Protein S total ag (%)	118,29 (± 17,36)	80 - 120
Anti beta2GPI IgG antibodies (U/ml)	0,79 (± 0,58)	<8
Anti beta2GPI IgM antibodies (U/ml)	0,95 (±1,08)	<8
Anti CL IgG antibodies (U/ml)	0,99 (± 0,72)	<10
Anti CL IgM antibodies (U/ml)	1,50 (± 1,36)	< 10
dRVVT (sec)	35,27 (± 2,90)	26 - 45
aPTT-LA (sec)	30,03 (± 8,62)	32 - 43
EXTEM		
CT (sec)	74,14 (± 11,01)	38-79
CFT (sec)	88,57 (± 13,95)	34-159
MCF (mm)	64 (± 3,30)	50-72
INTEM		
CT (sec)	224,50 (± 34,43)	100-249
CFT (sec)	85,57 (± 13,00)	30-110
MCF (mm)	62,29 (± 3,58)	50-72
FIBTEM		
MCF (mm)	17,79 (± 3,40)	9-25

PO087

URINARY POC TESTING FOR MEASUREMENT OF DOAC IN AN EMERGENCY CLINICAL SETTING: REAL WORLD DATA

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Background and Aims: With the increased use of direct oral anticoagulants (DOACs) and availability of reverse therapy, the need has arisen for a rapid test that would allow the assessment of clinically relevant plasma levels to manage the patient in emergency room. The aim of our study was to determine the feasibility and clinical utility of measuring DOAC levels by an urinary POC test which provides rapid and qualitative results. For this purpose, we repeated "a posteriori" a DOAC measurement by a quantitative standardized assay on plasma samples collected at the same time.
Methods: 53 patients admitted to the Emergency Department and Short and of the University Hospital of Careggi, Florence, and for whom clinicians requested the rapid assessment of DOAC levels, were recruited for this study. DOAC levels were determined by DOASENSE (Heidelberg, Germany) dipstick on urine and by commercial kits (Werfen) on plasma.
Results: In 9 patients (17%) Dipstick results were undetermined: in 7 samples (13.2%) for "creatinine levels low" and in 2 samples (3.8%) for a possible presence of interfering substances able to determine a positivity in both anti-Xa and anti-IIa drugs. As regards as the remaining 44 patients, Table 1 shows the concordance between the two methods. The False Negative (FN) on anti-Xa may be ascribed to the presence of haematuria; the FN on anti-IIa was likely related to an improper urine collection on catheter drainage bag positioned several hours before. In the 5 False Positive (FP) samples, we detected anti-Xa plasma levels close to the cut-off value of 30 ng/mL.
Conclusions: In an emergency clinical practice, the technical features of the test made it not usable in a non-negligible proportion of patients. In the remaining cases, our experience confirmed that it is a simple and effective way to rapidly detect the presence of clinically relevant DOAC levels. However, in 5 FP cases the quantitative dosage would have led to different clinical choices.

Table 1.

	FXa	THR
n (tot. 53, %)	36 (67.9)	8 (15.1)
Age, years (median, IQR)	82.5 (76.7-88.3)	82 (78.5-86.5)
DOAC Dipstick		
TP (n, %)	25 (69.4)	7 (87.5)
TN (n, %)	5 (13.9)	0
FP (n, %)	5 (13.9)	0
FN (n, %)	1 (2.8)	1 (12.5)

TP: True Positive, defined as DOAC Dicpstick positive with plasma DOAC concentration >30 ng/mL; TN: True Negative, defined as DOAC Dipstick negative with plasma DOAC concentration <30 ng/mL; FP: False Positive, represents a positive DOAC Dipstick in a patient with plasma DOAC concentration <30 ng/mL; FN: False Negative, represents a negative DOAC Dipstick in a patient with plasma DOAC concentration >30 ng/mL.

PO088

AN UMBRELLA REVIEW OF THE TOTAL THROMBUS-FORMATION ANALYSIS SYSTEM (T-TAS) AR-CHIP ON MONITORING ANTICOAGULANT THERAPY

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Background and Aims: The total Thrombus-Formation Analysis System (T-TAS) is an automated microchip flow-chamber system designed to evaluate whole blood thrombogenicity mimicking blood flow and observing how blood clots form on a special surface under controlled conditions. For example, the AR chip, coated with collagen and tissue factor, simulates atheroma's microenvironment. Our review aims to evaluate the literature about the T-TAS AR-chip performances for monitoring the anticoagulant effects of oral direct oral anticoagulants (DOACs) and Warfarin).
Methods: We searched the keyword "T-TAS" in the databases Google Scholar and Pubmed, including all articles about monitoring anticoagulation drugs on the AR-chip published until December 2023. The results of our research are summarized in the Table 1. We selected all the papers, excluding book chapters and theses. For the writing of this abstract, we followed the PRISMA 2020 guidelines.
Results: Our review encompasses 27 studies that have examined the clinical performances of T-TAS with AR-chip across a wide range of patients and settings. The heterogeneity of the studies in this review reflects the diverse contexts in which T-TAS has been investigated. Most of the studies focused on patients taking preventive or therapeutic anticoagulants for pulmonary thromboembolism, atrial fibrillation, stroke, or post-surgical procedures. T-TAS area under the curve (AUC) indicates clotting potential, which is crucial for assessing anticoagulant therapy efficacy. According to one of the studies (Ishii 2017), lower AUCs suggest effective anticoagulation, correlating inversely with DOAC plasma concentrations in atrial fibrillation. Moreover, some works (Iwanaga 2021; Hosokawa 2020; Sueta 2018) show that T-TAS can also be useful in predicting periprocedural bleeding and evaluating the long-term bleeding risk (Yamazaki 2020). Several studies explore how the T-TAS compares to standard coagulation tests like PT-INR and aPTT. Sueta's study found that T-TAS AUC levels are more effective predictors of DOAC efficacy than PT-INR and aPTT after knee arthroplasty. Matsuo's investigation yielded congruent findings among anticoagulated Fontan's syndrome patients, wherein PT-INR and APTT assessments were inadequate to find reductions in thrombogenicity. At the same time, T-TAS-derived AUC measurements emerged as a more effective evaluative parameter. Notably, other investigations about T-TAS utility in assessing concen-

trations of DOACs showed contrary findings. Taune's 2017 research found no correlation between DOAC concentrations and T-TAS variables, indicating that T-TAS primarily detects disparities in patients' hemostatic profiles. Rossi's study in 2020 revealed limited concordance with thromboelastogram, underscoring potential challenges in T-TAS's applications.

Conclusions: In summary, most studies indicate that the T-TAS with AR-chip is valuable for assessing bleeding risks during therapy and monitoring alterations in hemostasis induced by anticoagulation therapy with DOAC and Warfarin. However, further research is warranted to corroborate this assertion. A potential limitation of our study is the use of a single keyword for literature search, which may have impacted the comprehensiveness of our findings.

Table 1.

Articles excluded by:	Databases		Total Articles included	Articles Type				
	Google scholar	Pub med		Case reports	Original articles	Letter Editor	Review	Abstract/ Posters
	499	34						
Title	153	20						
Abstract	80	13						
Article	20	13						
Redundant			6	0	6	0	0	0
Articles included			27	0	18	4	2	3

PO089

STATINS AND VENOUS THROMBOEMBOLISM

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Venous thromboembolism (VTE) is the major causes of morbidity and mortality worldwide, after neoplasms and cardiovascular diseases. Approximately 10-30% of patients will die within the first month of diagnosis and sudden death is the first symptom in approximately a quarter (25%) of PE patients. Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are currently the only validate drugs for treatment of acute and long-term VTE, but they were affected by the risk of bleeding. An ideal drug should be able to reduce the risk of VTE recurrence without increasing the risk of major bleeding and mortality. There are several studies that highlight the ability of statins to decrease the rate of a first episode of VTE, the risk of VTE recurrences and death. There are conflicting data on the influence of statins on major bleeding during anticoagulation for VTE. The biological plausibility of the protective role of statins during anticoagulation has been demonstrated in several studies. Statins are able to influence the components of blood clotting such as D-dimer levels, tissue factor (TF) gene expression, coagulation factors VIII, VII and Von Willebrand. There is a growing interest on the antithrombotic properties of statins. Despite this, data supporting their use for the prevention of venous thromboembolism are not consistent and the impact of statins on VTE is still debated. Their presumed protective role against VTE is a matter of debate and needs to be further clarified by studies specifically conducted on this topic.

PO090

CHOLECYSTITIS AND VISCERAL THROMBOSIS: PARTNERS IN CRIME

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Background: Portal vein thrombosis (PVT) is a rare disease with an estimated incidence of 2 to 4 cases per 100,000 inhabitants. The most common predisposing conditions for PVT are chronic liver diseases (cirrhosis), primary or secondary hepatobiliary malignancy, major infectious or inflammatory abdominal disease, or myeloproliferative disorders. Several types of abdominal inflammatory diseases can be risk factors for the development of PVT. Below we report a case series on 3 cases of patients suffering from visceral venous thrombosis in patients with a clinical diagnosis of acute cholecystitis.

Case Report: A 54-year-old patient was admitted to hospital for fever and abdominal pain in the right hypochondrium. The abdominal ultrasound confirmed the presence of acute lithiasis cholecystitis, and it highlighted a left intrahepatic branch PVT. The patient was firstly treated first with fondaparinux and subsequently switched to direct oral anticoagulant (DOAC) (apixaban 5 mg BID) for 6 months. Upon ultrasound resolution of the PVT, cholecystectomy was performed, and anticoagulant therapy was stopped 2 months later. At one year follow-up, the patient did not present thrombotic recurrence. The second patient was a 73-year-old male diagnosed with acute cholecystitis and with CT finding of PVT of the intrahepatic branches and the common trunk. After 10 days of injection therapy with low molecular weight heparin he was treated for 6 months with rivaroxaban, without complications, with the complete resolution of the thrombosis. Cholecystectomy was subsequently performed. The third patient is a 92-year-old man, hospitalized for a syncope and sepsis. On abdominal ultrasound, cholecystitis with pericolecystic abscess was found and a floating thrombus was found in the middle hepatic vein. Anticoagulant therapy with heparin SC 6000 IU BID was introducedDuring hospitalization, the patient underwent antibiotic therapy and ultrasound-guided needle aspiration of the pericholecystic abscess. At the 7-day ultra-

sound check, the thrombus in the middle hepatic vein was no longer evident. The patient was treated for 3 months with full-dose low molecular weight heparin, with subsequent stop of full-dose therapy and prescription of prophylaxis in consideration of chronic bed rest. Thrombophilia screening was negative in each patient, including screening for antiphospholipid antibodies. As a co-risk factor for thromboembolism, the first patient had grade II obesity.

Conclusions: Acute cholecystitis is a risk factor for the development of porto-mesenteric and hepatic vein system thrombosis. The initial therapeutic choice was almost exclusively on parenteral therapy with heparin or fondaparinux. In none of our 3 cases a vitamin K antagonist was prescribed, and in the 2 cases that switched to oral anticoagulant therapy, DOAC was preferred. Although no cases of bleeding complications have been reported, the presence of venous thrombosis induces a delay in the definitive surgical treatment of cholecystitis (cholecystectomy). After adequate therapeutic timing (although different from case to case) there was a complete resolution of the thrombosis on diagnostic imaging.

PO091

PREDICTIVE VALUE OF D-DIMER IN THE DIAGNOSIS OF VENOUS THROMBOEMBOLISM (VTE) IN ELDERLY HOSPITALISED PATIENT: A SINGLE-CENTER RETROSPECTIVE OBSERVATION

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Background and Aims: The use of d-dimer in venous thromboembolism (VTE) exclusion strategies has been widely validated. However, there are many conditions that can cause an increase in d-dimer values, such as advanced age and hospitalisation. In these cases, elevated d-dimer levels could lead to an excessive demand for diagnostic tests to rule out VTE. The aim of our study is to evaluate the predictive role of d-dimer in ruling out VTE in elderly hospitalised patients.

Methods: Patients >60 years of age admitted from January 2021 to December 2022 who had a venous ultrasound-Doppler performed for suspected deep vein thrombosis (DVT) were included. SPSS29 software was used for the statistical analysis. Comparison between categorical variables was performed with Chi-square tests. ROC curves were used to search for new D-dimer cut-offs. All calculations were estimated with the 95% confidence interval calculated with the distribution-free method and the significance level of the statistical tests was set at 5%.

Results: 169 patients (mean age 86±25 years) were included. More than ⅔ of participants were women (67.46%). D-dimer was measured in 70 (41%) patients. In patients with diagnosis of VTE, d-dimer was measured in 42% of cases. In patients without diagnosis of VTE, d-dimer was measured in 41% of cases. In ROC analysis, the area under the curve (AUC) was 0.64, suggesting poor test performance (Figure 1).

Conclusions: In our population, d-dimer testing showed no predictive value in elderly hospitalised patients.

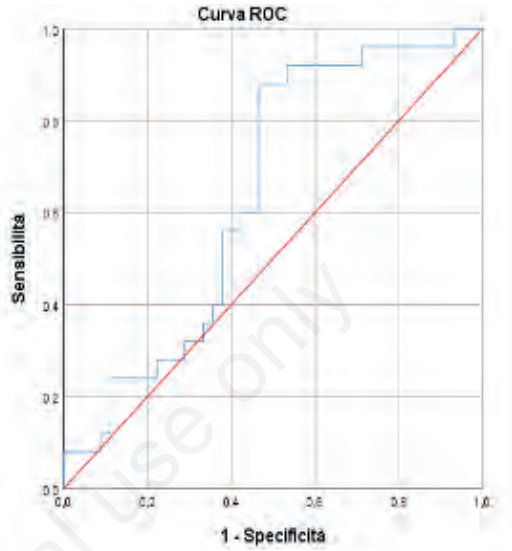

Figure 1.

PO092

PROPOSAL OF MANAGEMENT OF THROMBOSIS IN PATIENT AFFECTED BY SARCOIDOSIS: A CASE REPORT

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Background: Autoimmune/autoinflammatory disorders (AD/AID) are associated with arterial or venous thrombotic events (VTE). Chronic inflammation and immune system impairment lead to endothelial damage, coagulation cascade activation, fibrinolytic system injury, platelet activation, and blood flow alterations, all of these able to induce the thrombotic process. Based on the literature, AID have an intermediate risk for long-term VTE recurrence (3-8% per year) so that the European guidelines suggest indefinite anticoagulation therapy in this setting. However, the risk of VTE varies according to the type and stage of the rheumatic disease and to the concomitant treatments. Actually, clinical trials investigating the optimal duration and type of oral anticoagulants in patients with AD are lacking, Sarcoidosis is an inflammatory noncaseating granuloma disease affecting lungs, lymph nodes, liver, skin and eyes. As well as other AD/AID, sarcoidosis show an increased risk of developing VTE. Although usually sarcoidosis turn it in a chronic disease, complete remission occurs in about 30% of

cases. Therefore, is it possible to hypothesize to discontinue anticoagulation when sarcoidosis heals? Here, we report the case of a sarcoid patient arose with splanchnic thrombosis treated with warfarin as long as clinical and instrumental data reported remission of the AID.
Case Report: In May 2022 a 52-year-old woman was admitted to the emergency department for hematemesis: gastroscopy showed congestive mucosal of the gastric wall whereas abdominal CT scan revealed an acute full thrombosis of the mesenteric, splanchnic and portal veins. Her past medical history was unremarkable. The laboratory work-up was negative for inherited or acquired thrombophilia. However, considering the severity and the atypical location of the thrombosis, in order to exclude concomitant malignancy, she underwent PET-CT which evidenced high intensity signal on lateral cervical and subclavian lymph nodes. The histologic examination revealed non-caseating granulomas without evidence of malignancy or infectious organisms. The patient was diagnosed with clinically asymptomatic sarcoidosis arose with splanchnic thrombosis and discharged with warfarin. After one year of treatment she asked to stop anticoagulant: she was advised to repeat the abdominal angio-CT and the PET-CT. The first revealed a complete reperfusion of the splanchnic veins while the latter showed an increased number of lymph nodes involved. Although the patient was still asymptomatic for sarcoidosis, bacause of the worsening of the AID, she was advised to continue anticoagulation and to repeat PET-CT the next year.
Conclusions: Sarcoidosis is a prothrombotic disease as well as other autoinflammatory conditions. When VTE occurs, antithrombotic treatment is mandatory. However the duration of the therapy is not clear but according to guideline recommendations, anticoagulants should be continued long-term. Nevertheless, what to do in case of complete recovery from the AD? In the absence of scientific evidence, here we propose our approach to thrombosis in sarcoid patients (Figure 1).

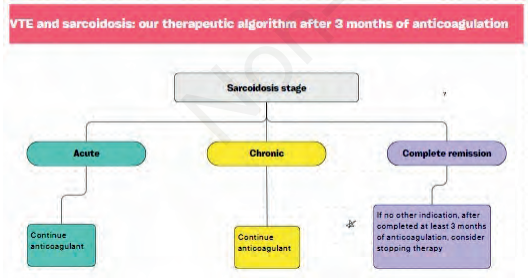

Figure 1.

PO093

STRATEGIES AND CONSIDERATIONS IN THE MANAGEMENT OF SAPHENO-FEMORAL AND SAPHENO-POPLITEAL JUNCTION THROMBOSIS: A CASE SERIES

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Background: Superficial vein thrombosis (SVT) of the limb is a common condition. According to the latest guidelines, anticoagulant therapy with low-dose fondaparinux provides effective protection against recurrence, with negligible bleeding risk. The extension of SVT within 3 cm of the sapheno-femoral (SFJ) or sapheno-popliteal junctions (SPJ) is a therapeutic conundrum. Management usually involves therapeutic dose of anticoagulant therapy, although guidelines on the topic are elusive. We present a case series of patients with extended SVT, in which we evaluated the efficacy and safety of customised doses and duration of anticoagulant therapy.
Case Report: Between March 2022 and December 2023 we followed 9 patients (4 women, 44.4%; median age 60 years, interquartile range [IQR] 54-74) with documented SVT extended within 3 cm of the SFJ or SPJ. Diagnosis was made with compression ultrasonography. All the patients received fondaparinux, administered subcutaneously at therapeutic dose according to body weight once daily until the first follow-up visit. After a median of 15 (IQR 13-15) days from diagnosis, In 7 patients (77.8%) no further involvement of the SFJ or SPJ was detected and they were switched to fondaparinux at a dose of 2.5 mg once daily for a median of 34 (IQR 27-44) days. Local extension of SVT occurred in 1 patient (11.1%) after 22 days from switch to fondaparinux 2.5 mg. After discontinuation of fondaparinux 2.5 mg, two patients experienced a recurrence of extended and non-extended SVT after 28 and 92 days, respectively. The patient with extended SVT was treated with a therapeutic dose of rivaroxaban, while the other patient was treated with a reduced dose of fondaparinux followed by sulodexide for secondary prevention. No one experienced bleeding events or death from any cause.
Conclusions: In this case series we observed that reduced doses of anticoagulants, once the superficial vein thrombosis is ≥3 cm away from the SFJ or SPJ, seems to be non-inferior to therapeutic anticoagulant dose of fondaparinux in preventing thromboembolic complications with comparable safety.

PO094

SEPTIC PORTAL VEIN THROMBOSIS, CLINICAL PRESENTATION, AND MANAGEMENT

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Background: Pylephlebitis, or infective thrombophlebitis of the portal vein, is a rare and underdiagnosed condition which can complicate any intra-

abdominal or pelvic infections in areas drained by portal venous circulation. It should be considered early on any patient presenting fever, abdominal pain, leukocytosis and CT scan evidence of portal vein thrombosis. Pylephlebitis can easily be treated with early antibiotic and anticoagulating therapy, so it's imperative to consider it in differential diagnosis of intra-abdominal infections. They should be administered in patients with thrombosis progression or persistent fever to increase the rates of thrombus resolution or decrease the overall mortality. This case report will present a subject suffering pylephlebitis.

Case Report: A 64-year-old male patient was admitted to our hospital because of persistent fever from about 6 days, treated by ciprofloxacin 500 mg x 2/day, with no appreciable benefit. The patient's medical history is significant for previous melanoma, kidney stone surgery, arterial hypertension on treatment, newly diagnosed segmental colitis diverticulosis associated (SCAD), BPH.

Labs revealed leukocytosis (22,10 x103 /uL) with significant neutrophilia and high levels of procalcitonin, total protein, liver transaminases, alkaline phosphatase (ALP) and C-Reactive Protein (CRP). The international normalized ratio (INR) was 1.32. Abdominal ultrasound was performed, showing mild hepatomegaly with evidence of focal lesions in the V segment compatible with abscess formation and a parenchymal cyst in the VI segment. A computed tomography (CT) abdomen/pelvis with intravenous contrast was ordered. The scan demonstrated rounded hypodensities between the V and VI hepatic segment, the first hypothesis included liver abscesses. There was intrahepatic sectoral thrombosis of the right branch of the portal vein (S5-S6) in proximity to the hepatic abscess formation. After 20 days MRI with contrast also demonstrated the presence of thrombosis of the juxatalesional tract (V-VI segment) of the middle suprahepatic vein and a right portal branch. Wainting for blood culture results, prompt IV piperacillin/tazobactam and then Linezolid were started. There was no resolution of the septic state, so he underwent a radiology drainage of the multiple abscess collections. Blood cultures were positive for Peptostreptococcus anaerobius. Anticoagulant therapy with EBPM (Inhixa 6000 UI x 2) was introduced. The patient was discharged with Levofloxacina, amoxicillina/acido clavulanico until reassessment. The heparin therapy switched to warfarin after 3 months to avoid drug interactions.

Conclusions: Pylephlebitis or septic thrombosis of the portal vein is a rare diagnosis that should be considered in patients presenting with fever, abdominal pain, bacteremia, and evidence of portal vein thrombosis on imaging studies. The most common etiologies include intra-abdominal infections that spread into the portal vein. Hypercoagulable states and/or deficiencies in clotting factors are considered major risk factors for pylephlebitis, especially in the setting of sepsis, along with prior abdominal operations, smoking, malignancy, cirrhosis, and the use of steroids Treatment includes antibiotic therapy for several weeks, and the use of anticoagulation is still debated. But once diagnosed, all patients should undergo prompt antibiotic and anticoagulation therapy.

PO095

CLINICAL HISTORY OF PATIENTS WITH ISOLATED JUGULAR VEIN THROMBOSIS RECEIVING DIRECT ORAL ANTICOAGULANTS: A CASE SERIES

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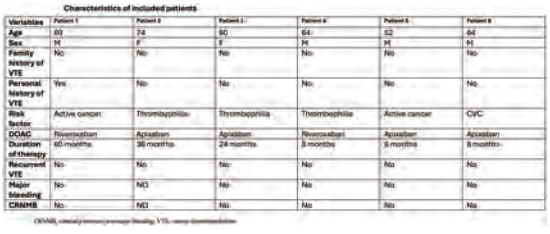
Background and Aims: Due to the lack of data on direct oral anticoagulants (DOACs), vitamin K antagonists (VKA) are usually recommended for the treatment of isolated jugular vein thrombosis. Some patients, however, occasionally receive DOACs for specific clinical reasons (*e.g.*, intolerance or poor compliance to VKA, difficulties in performing frequent follow-up). The aim of this study is to report the clinical history of patients with isolated jugular vein thrombosis who received DOACs.

Methods: We performed a preliminary retrospective analysis of patients prospectively followed in our outpatients' clinic from 2014 to 2024. Patients with jugular vein thrombosis were included if they did not receive VKA (*e.g.*, patients' intolerance, poor compliance, or refusing VKA) and if they were treated with DOACs. Baseline characteristics (*e.g.*, demographic, thrombotic risk factors), type and duration of anticoagulation, and outcomes of interest were descriptively reported. Effectiveness outcomes was recurrent VTE while safety outcomes were major and clinically-relevant non-major blessings.

Results: A total of 6 patients were included. Population characteristics are shown in Table 1. The mean age was 62 years and 33% of patients were female. One patient had a personal history of thrombosis while, in every included patient, there was no family history of thrombosis. Most of patients (50%) had thrombophilia as risk factor for thrombosis, while the 17% had an active neoplasm as a risk factor. The remaining cases (17%) had an unprovoked thrombosis. The most widely used DOAC was apixaban and the median treatment duration was 18 months (minimum 6 months, maximum 60 months). During follow-up there was no recurrent venous thromboembolism nor major or clinically relevant bleedings.

Conclusions: Our case series should suggest the effectiveness and safety of the DOACs as anti-thrombotic therapy for jugular veins thrombosis. Further studies in larger cohorts will be needed to confirm our data.

Table 1.



Characteristics of included patients

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	69	74	60	64	52	64
Sex	M	F	F	M	M	M
Family history of VTE	No	No	No	No	No	No
Personal history of VTE	Yes	No	No	No	No	No
Risk factor	Active cancer	Thrombophilia	Thrombophilia	Thrombophilia	Active cancer	CVC
DOAC	Rivaroxaban	Apixaban	Apixaban	Rivaroxaban	Apixaban	Apixaban
Duration of therapy	60 months	36 months	24 months	3 months	5 months	9 months
Recurrent VTE	No	No	No	No	No	No
Major bleeding	No	NO	No	No	No	No
CRNMB	No	NO	No	No	No	No

PO096

SPLANCHNIC VEIN THROMBOSIS: A CLOSER LOOK AT CAUSES AND COMPLICATIONS THROUGH A RETROSPECTIVE INSTITUTIONAL COHORT

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Background: Splanchnic vein thrombosis (SVT) is associated with many conditions, but the underlying cause remains unidentified in about 20% of cases. Recent studies suggest that clonal hematopoiesis of indeterminate potential (CHIP) may play a role. Moreover, despite treatment some patients progress to chronic thrombosis, characterized by complications like cavernomatosis. This retrospective study aims to improve understanding of SVT by analyzing clinical, instrumental, and laboratory data.
Materials and Methods: This study analyzed 47 patients with SVT admitted to our Division of Internal Medicine. Data were collected retrospectively, and included clinical and laboratory data, information about the causes, veins involvement, occlusion degree, cavernoma or varices presence, spleen size and thrombophilia state. Only a few patients provided information on liver and spleen stiffness. Histological data from bone marrow biopsy were collected when available.
Results: The cohort consisted of 25 males and 22 females, with a mean age of 58.6 years. 38% had no clear cause at diagnosis. At the conclusion of investigations, idiopathic cases were reduced to 23%. CHIP was identified in 9 cases, but no clinical differences correlated with a particular mutation were identified. Overall, SVT was attributed to myeloproliferative neoplasms (MPN) in 10 patients. One patient was initially diagnosed with CHIP, and after a four-year interval met the criteria for MPN.
A slight increase in the basophil count (mean difference [MD] +50/uL, p=0.004) was identified in patients with CHIP and a post-hoc analysis revealed that a basophil count >40/uL may be a risk factor for CHIP (OR 15, p=0.019). 21% of patients developed portal cavernomatosis, with an average onset of 6 months. Those with portal thrombosis in conjunction with mesenteric or splenic thrombosis had an increased risk for cavernoma development at the limit of significance (OR 4.9, p=0.052). Conversely, when the three veins were involved, a significant increased risk of developing cavernoma was observed (OR 13.5, p=0.003). 10 patients underwent liver and spleen elastography. Both liver (MD 2.5 kPa, p=0.011) and spleen (MD 67.3 kPa, p=0.005) stiffness were lower in patients with SVT resolution. In a post-hoc analysis, liver stiffness >6 kPa (OR 25, p=0.048) and spleen stiffness >60 kPa (OR 77, p=0.018) were associated with a risk of persistent thrombosis. Similarly, liver stiffness was greater in patients who developed portal cavernomatosis (MD 2.13 kPa, p=0.016), while both stiffnesses were greater in patients who developed esophageal varices (liver: MD 2.36 kPa, p=0.003; spleen: MD 64.6 kPa, p=0.001).
Conclusions: Our study suggests that a significant proportion of SVTs may have an underlying hematologic disorder that requires closer monitoring over time. The data requires further validation, but basophils may help clinicians identify suitable patients for hematologic investigation. The identification of surrogates to identify patients at risk for chronic complications is crucial. Consistent with this , the extension of SVTs to multiple veins may increase the risk of cavernoma development. Liver and spleen elastography may be beneficial in clinical monitoring of SVT patients limiting exposure to more invasive investigations. However, to better evaluate its usefulness, the cohort must be expanded and the timing of these tests calibrated.

PO097

QUADRUPLE ANTIPHOSPHOLIPID ANTIBODY POSITIVITY IS ASSOCIATED WITH ACCRUAL DAMAGE IN ANTIPHOSPHOLIPID SYNDROME SUBSETS

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Background and Aims: Antibodies against phosphatidylserine/prothrombin (aPS/PT) have received significant attention in diagnosing APS, particularly thrombotic APS. A strong association has been revealed between aPS/PT antibodies and thrombosis and pregnancy morbidity in APS patients, emphasizing the potential clinical utility of including aPS/PT antibodies in the diagnostic evaluation of APS, particularly in identifying individuals at higher risk for thrombotic events and adverse pregnancy outcomes. Here, we evaluate the association of aPS/PT antibodies with accrual damage in APS.
Patients and Methods: We conducted a monocentric exploratory cross-sectional study. The study included 143 patients fulfilling the ACR/EULAR 2023 classification criteria for APS. Immunoglobulin (Ig)G/IgM aPS/PT, IgG/IgM anticardiolipin (aCL), and IgG/IgM anti- β2 glycoprotein I (anti- β2 GPI) antibodies were detected using ELISA assay and lupus anticoagulant (LA) with a series of coagulation tests.
Results: IgG aPS/PT, but not IgM aPS/PT were associated with both arterial and venous thrombosis events (p=0.036) concerning arterial or venous thrombosis alone (42.9% *vs* 34.9% *vs* 22.2%). There was no difference between IgG/IgM aPS/PT and obstetric APS subsets. IgG and IgM aPS/PT were significantly associated with the microvascular domain (p=0.01 and p= 0.005, respectively), while IgG aPS/PT was associated with valvulopathy (p= 0.022). Both triple aPL positivity

(IgG/IgM aCL+IgG/IgM anti- β2 GPI +LA) and quadruple aPL positivity (IgG/IgM aCL+IgG/IgM anti- β2 GPI +LA) were associated with accrual damage (p=0.035 and p= 0.003, respectively). However, at the multivariate logistic regression, only quadruple aPL showed a 4-fold risk of accrual damage in APS patients (OR 4.2, 95%IC 1.1-16.4, p=0.038).
Conclusions: Our data attribute clinical relevance to both IgG and IgM aPS/PT antibodies. Both IgG and IgM aPS/PT were associated with more severe APS subsets, such as the presence of arterial and venous thrombosis, as well as the microvascular and valvulopathy domains. Moreover, quadruple aPL positivity was associated with accrual damage, suggesting their utility in risk stratification in APS patients.

PO098

LONG TERM PROPHYLAXIS IN PATIENT WITH TYPE 2 VON WILLEBRAND DISEASE: A CASE REPORT

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Background: Von Willebrand disease (VWD) is the most common inherited bleeding disorder. Multiple subtypes exist and require individualized treatment based on specific diagnosis, bleeding phenotype, and specific clinical context. Major therapies include use of desmopressin to induce endothelial release of stored von Willebrand factor (VWF) and factor VIII (FVIII) and use of VWF concentrates, as well as adjuvant therapies, such as antifibrinolytic tranexamic acid. Guidelines and recommendations for prophylaxis and treatment of bleedings in vWD patients with vWF/FVIII concentrates should be derived from analysis of the content of concentrates and from pharmacokinetic studies in different types of vWD patients with severe type 1, 2, or 3 vWD.
Case Report: A 70-year-old patient has been diagnosed with von Willebrand's disease type 2B since 1999. Following Sanger sequencing of exon 28 of von factor Willebrand, the c.4613C>G nucleotide substitution in heterozygosity (p.Thr1538Arg mutation) was highlighted. This mutation, previously identified in a family member of the patient, has not been previously reported in the literature. During his childhood and youth he had several frequent episodes of epistaxis, spontaneous bruising, and prolonged bleeding in the case of wounds. at the age of 67 he had an episode of hematuria after placement of a bladder catheter. In 2020 he had cerebral hemorrhage after head trauma. Since 2021 he has reported episodes of recurrent gastrointestinal bleeding due to angiodysplasia of the small intestine, which have required several hospitalizations, blood transfusions and infusions of FVIII/vWF concentrates. Furthermore, the patient underwent embolization of a Dieulafoy lesion in an atypical location. Laboratory tests showed: FVIII:C 79%, VWF:Ag 94%, VWF:RCo 12%, absence of high molecular weight multimers. In consideration of recurrent GE hemorrhagic episodes and severe anemia we proposed a long term prophylaxix with von Willebrand factor plasma concentrate (Wilfactin®) at a dosage of 2000 UI three times a week. From January 2024 the administration timing has been reduced to twice a week. The patient has been following the prophylaxis regimen for a year and has no longer had any bleeding episodes (Table 1).
Conclusions: Management of patients with von Willebrand disease remains challenging because of variability in individual patient bleeding symptoms in clinical practice, and lack of high-certainty evidence to guide decision making.

Table 1.

Laboratory tests	
PT/INR	1.01
aPTT ratio	1.25
Fibrinogen	281 mg/dl
FVIII:C	57%
VWF Ag	48%
VWF:RCo	12%
Binding Collagene	16%
PFA Coll/ADP	205 sec
PFA Coll/EPI	>211 sec
HMW	absence

PO099

TWO BROTHERS: A COMMON COAGULATION DEFECT, TWO DIFFERENT OUTCOMES

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Background: Factor XI deficiency is a rare recessive autosome with variable penetrance inherited disorder of coagulation, known as Haemophilia C. The general population incidence is 1 in a million but it appears to be more common amongst Aghkenazi (East European) Jews (heterozygote frequency of 8-10%). The phenotypic expression is usually mild and the bleeding events are usually provoked. The laboratory marker associated with the disease is prolonged aPTT, as such as the other coagulation anomalies of the intrinsic coagulation pathway. Factor XI deficiency is a practical and conceptual challenge for clinicians, due to poor correlation between factor level and symptoms, different bleeding diathesis of different tissues and weak available data due to its rarity. Severe spontaneous bleeding is rare, although menorrhagia and epistaxis may be quite common, while traumatic triggered bleedings are frequent, if the trauma involves oral and/or nasal cavities or urinary tract. The bleeding risk of invasive procedures is controversial, though most of the procedures seem to be well tolerated without factor replacement treatment. To date, we do not have indications about the use of direct oral anticoagulants in Factor XI deficiency patients.
Case Report: We present the case of two brothers with

the same coagulation genetic defect but two different outcome. The eldest, with known atrial fibrillation, was not in anticoagulation therapy, despite his CHA2DS2 VASc score was 2 because of mild factor XI deficiency (51%). He was submitted to two ineffective electrical cardioversions in 2019. In May 2023 during a trip to Liguria, he had posterior acute ischemic stroke complicated by post traumatic cranial trauma with subarachnoid bleeding. He was then admitted to our Hospital and started anticoagulation therapy with dabigatran as soon as clinical and radiological improvement of subarachnoid bleeding was demonstrated. No haemorrhagic complications has been recorded so far (one year follow-up). The youngest underwent our Hemostasis Center evaluation in 2017, his factor XI level was 38% and he had atrial fibrillation resistant to ablation strategy (CHA2DS2 VASC 2). The case has been discussed for left atrial appendage closure but the shared decision was to start anticoagulation treatment with Dabigatran without any complication.
Conclusions: The factor XI deficiency is a rare and not linear coagulation defect due to poor correlation between the amount of FXI and clinical expression. These variable scenarios can be challenging for clinicians, like delivery or the major surgical procedures or the use of drugs as antiplatelet agents in single or dual use or anticoagulant use as vitamin K antagonists or direct oral anticoagulants.

PO100

ACCIDENTAL FEMUR FRACTURE DISCLOSING A RARE BLEEDING DISORDER

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Background: Factor V (FV) deficiency is an extremely rare autosomal recessive disorder occurring in 1:1000000 of the population (1), also known as Owren disease. It is associated with mild to moderate bleeding tendency usually consisting in mucocutaneous bleeding. Diagnosis of factor V deficiency is suspected with both thromboplastin time (TP) and activated partial thromboplastin time (aPTT) prolongation and a normal thrombin time (TT), but definitive diagnosis made by factor V assay is crucial to achieve the correct diagnosis. Clinical presentation may vary depending on the severity of Factor V levels, but bleeding tendency does not well correlate with FV levels (2). Accurate diagnosis of factor V deficiency is necessary to prevent spontaneous and surgical bleeding complications.
Case Report: A 73-year-old woman presented to our emergency department with a post-traumatic femur fracture. Urgent laboratory tests showed abnormal TP (4.3 ratio) and aPTT (4.6 ratio) prolongation and D-dimer marked elevation. A vitamin K intravenous administration did not modify the coagulation test results. An abdomen ultrasound didn't show liver cirrhosis or any hepatic morphological alteration, while a lower extremity ultrasound excluded deep vein thrombosis. As a further diagnostic workup Factor II, Factor X and factor V essay were performed, resulting in severe Factor V deficiency (2%). A detailed family and past medical history evaluation did not reveal any bleeding tendency even in absence of major or significant surgical procedures. In order to avoid any bleeding complication related to the orthopedic surgery, 15 ml/kg Fresh Frozen Plasma was safely administered, and the patients underwent surgical femur reduction and internal fixation. Subsequent clinical course was characterized by hemodynamic stability. In relation to the persistence of moderate anemia, surgical wound serous leaking and persistent prolonged TP and aPTT, no heparin prophylaxis was performed. Laboratory tests in patient's son confirmed the presence of mild TP and aPTT prolongation and a slighter factor V deficiency (58%).
Conclusions: Factor V deficiency is a rare coagulation defect. It can present both silently or via mild to moderate bleedings. Preemptive prediction of bleeding complications is difficult in relation to the different inter-individual clinical presentation. Prompt identification of this disorder through accurate laboratoristic workup is essential to prevent bleeding complications, especially in patients undergoing major surgical procedures.

PO101

PORTAL VEIN THROMBOSI (PVT) SECONDARY TO DEFICIENCY C PROTEIN IN A YOUNG MALE

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Premises: Inherited defects of the natural coagulation inhibitors predispose patients to thrombosis. These disorders have similar clinical presentations with a strong family of thrombosis, episodes of recurrent venous thromboembolism, beginning in early adulthood. We report a case of portal vein thrombosis (VPT) secondary to hereditary protein C deficiency in a young male.
Case Report: A 39-year-old male was admitted to the hospital for abdominal pain. Laboratory tests revealed levels of alanine and aspartate aminotransferases increased and levels of lipase and amylase normal, ruling out any possibility of pancreatitis. Abdominal CT scan indicated thrombosis of the portal vein and multiple celiac lymph nodes. There were attempts to pinpoint the origin of the clot. To exclude occult malignancy PET/CT scan was conducted. Results from viral profiles and tumor markers were negative. Cardiolipin and antiphospholipid lipid antibodies produced negative findings. The levels of antithrombin III were normal, and the Factor V Leiden mutation was unremarkabl. Low levels of protein C (PC) antigen (28% with n.r. 70-140%) and normal protein S antigen activity were found. Therefore, insufficient PC came out to be the primary cause of PVT. The patient

was prescribed anticoagulant therapy with fondaparinux 7,5 mg/die and then warfarin for a long period to target an INR range of 2-3.
Conclusions: Inherited PC deficiency is rare in PVT. Its identification is important for treatment of PVT, with better outcomes associated with early anticoagulant medication intervention.

PO102

PROPHYLAXIS FOR DENTAL CARE IN A PATIENT WITH LIGNEOUS GINGIVITIS DUE TO PLASMINOGEN DEFICIENCY

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Background: Congenital plasminogen (PLG) deficiency is a rare autosomal-recessive disorder of the fibrinolytic system associated with abnormal accumulation of fibrin-rich pseudo-membranous lesions on mucous membranes. Most common clinical manifestations are ligneous conjunctivitis (LC) and ligneous gingivitis (LG), but pseudo-membranes could also interest central nervous system, ears, nasopharynx and respiratory, gastrointestinal and genitourinary tracts. LC can lead to blindness, while LG to periodontal disease causing loss of teeth, with an high impact on quality of life. LG can occur spontaneously but seems to be triggered by minor trauma or infections. Currently, no specific replacement therapy is available in Italy, even if a plasminogen concentrate has been approved by FDA. There is no consensus on management of LC and LG. Several topical and systemic approaches have been suggested, including prophylaxis with fresh frozen plasma (FFP) and heparin.
Case Report: A 33 years old (yo) woman was referred to our centre in 2019. She was diagnosed with LC at age of 9 in France, treated successfully with autologous buccal mucosa graft. Oral mucosal lesions started when she was 12 yo, leading to loss of various teeth in the following years. At presentation, the patient (pt) already losses 6 teeth and presented parodontopathy and mobility of the other teeth. Plasminogen levels were 19% (normal range 80-110%), due to a double heterozygous mutations of the PLG gene p.Arg386* and p.Trp616Cys. The pt reported spontaneous regression of gingival pseudo-membranes after a tooth loss. Thus, we approached the extraction of four teeth, in three different sessions, without any prophylaxis. No complications occurred during ad after the procedure, and pseudo-membranes, previously surrounding the dental elements, gradually regressed. Dental implants were postponed after gum healing. The first intervention was done with a single dental implant, and the second with three implants in the same session. In both instances, a prophylactic treatment with FFP 10 mL/Kg was performed, just before the procedure and after 24 hours, without complications and with no formation of new pseudo-membranes. Measured PLG levels were: basal level 18%; 30% after first FFP infusion and 26% 24 hours after; 38% after the second FFP infusion and 32% 24 hours after the second and last FFP. Interestingly, pt reported that a pseudo-membrane present in a different site of the gum detached after FFP infusion and reappeared four days later. After a follow up of two years, all implants are in good conditions without evidence of pseudo-membranes surrounding the sites of intervention. Some small pseudo-membranes are still present near other teeth without affecting their stability.
Conclusions: PLD deficiency is a very rare defect with limited therapeutic option. Due to its rarity, no guidelines nor consensus are available to manage the complications. Advanced LG could lead to the loss or to the need to remove dental elements. Our experience suggests that dental extraction doesn't request any prophylactic treatment, leading to gum healing probably due reduction of inflammation. We used prophylaxis with FFP for dental implant with the aim to reduce the probability of excessive fibrin accumulation leading to formation of new pseudo-membranes. Unlike previous reports, we did not administer heparin, with good results.

PO103

NOONAN SYNDROME: NOT ONLY-A-CARDIOLOGIST JOB

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Background: Noonan syndrome (NS) is a rare autosomal dominant disease withsystemic involvement most oftern represented by cardiovascular abnormalities requiring surgical correction. However, in 30-72% of cases, NS can be associated with bleeding disorders including clotting factors (CF) deficiencies and/or platelets disorders.
Case Report: We present the case of 13 years old male patients admitted for for heart failure secondary to severe aortic valve regurgitation in evaluation for cardiac surgery; he was evaluated by hematologist for moderate macrocytic anemia (Hb 9g/dl, MCV 100.8fL, MCH28). Past medical history was significant for hemorrhagic diathesis with 3 episodes of epistaxis, one of them requiring emergency room access. The coagulation assessment showed a prolonged PT-INR (1.4), no aPTT and fibrinogen abnormalities; the study of clotting factor (CF) showed only mild FVII:C deficiency (34%, other CF and parental FVII:C normal). Platelet function was not investigated.. At that moment the patient was deemed not eligible for cardiac surgery due to extremely high perioperative bleeding risk. The patient was subsequently evalu-

ated by an hematologist specialized in hemostasis and thrombosis sp and a global evaluation of clotting function was performed; the anemia was corrected with supportive therapies and a pre-operative administration of plasma-derived FVII was administeredto reduce the risk of major perioperative bleeding. The patient was successfully treated with open-heart aortic valve repair with Ozaki technique after infusion of plasma-extracted FVII before the extracorporeal circulation (with normalization of PT-INR and FVII:C of 80%) and subsequently received a three months course of oral anticoagulation therapy with vitamin K antagonist (VKA) without hemorrhagic complications (a close hematochemical and clinical monitoring was performed in our centre). 3 months after surgery the patient showed resolution of symptoms related to heart failure (NYHA I) and no further episodes of epistaxis (a local cauterizations was performed before surgery).

Conclusions: Patients affected by NS often require cardiac surgery evaluation and concomitant bleeding disorders may substantially increase perioperative mortality risk and severely affect life quality thus reducing. A comprehensive clinical and biochemical evaluation should be carried out both at diagnosis and prior to any surgical procedures and bleeding risk must be carefully even in the case of unremarkable or mildly abnormal coagulation tests. This evaluation is of utmost importance in patients with NS undergoing cardiac surgery in order to safely perform the procedure and improve patient outcome.

PO104

EFFICACY AND SAFETY OF RECOMBINANT FACTOR XIII AFTER 10 YEARS OF THERAPY

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Background: Congenital deficiency of Factor XIII (FXIII) is an autosomal recessive alteration that has a prevalence of about 1 case per million people and is equally distributed in both genders. Factor XIII consists of 4 subunits (A2B2), the B subunits act as carriers, while the A units have a catalytic function. Congenital deficiency of FXIII affects subunit A and results in symptomatology that is dependent on the plasma level of the factor and can go as far as severe spontaneous intracranial hemorrhage. The first manifestations can occur as early as birth, with cord bleeding, or in the first years of life, with spontaneous muscle hematomas, with a typical location of ileo-psoas. Until 2013, plasma-derived Factor XIII had been used, then replaced by recombinant subunit A, which binds to the circulating subunit B, reconstituting the functionality of the whole molecule. An Italian retrospective study by Ezio Zanon on 20 patients showed that the dose of 35 IU/kg administered prophylactically every 28 days was able to maintain a sufficient level of FXIII, while avoiding significant hemorrhagic symptoms.

Case Report: Our aim was to test, in a 37-year-old patient already included in Zanon's study, whether the protective effect of Catridecacog was maintained after 10 years of therapy. The patient had had spontaneous hemorrhage of the ileo-psoas at 12 years of age; he was previously treated with Fibrogammin and started Catridecacog administration in 2014. He had had a major hematuria episode in 2010, due to the 2-month delay of Fibrogammin administration. He currently weighs 80 kg, so the administration of one vial of 2,500 IU corresponds to the dose of 31 IU/KG. The patient had no side effects or hemorrhagic events. In the second half of 2023, we dosed the level of FXIII on the days following the administration of three doses of FXIII and used the values obtained on different days to construct a plasma concentration trend curve. In case of dosing on corresponding days, we evaluated the mean of the values obtained. Our findings showed the following: 1) The plasma level of FXIII, measured 2 hours after administration, was 80%. On subsequent days we had 52.6 at 48 hours, 41 at 4 days, 22.3 at 10 days, 9.5 at 20 days, and 6 at 28 days. We always had a functionally sufficient value until the time of the next dose (Figure 1). 2) Comparing the data collected after the different administrations, we found a high reproducibility of the results. The individual values obtained on the corresponding days, indeed, never deviated from the average of that day by a percentage greater than 15%.

Conclusions: Administration of recombinant FXIII, after 10 years of therapy, was found to be safe; assay of plasma levels demonstrated the maintenance of effective levels throughout the observation period.

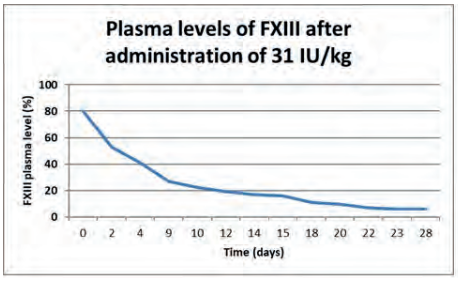

Figure 1.

PO105

CURRENT DIAGNOSIS OF VWD IN ITALY: THREE YEARS FOLLOWING THE RELEASE OF THE INTERNATIONAL GUIDELINES

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The ASH-ISTH-NHF-WFH-2021 International Guidelines (IGL) on von Willebrand disease (VWD) have pointed out many challenges, mainly in the diagnostic approach of VWD patients. Despite many attempts by experts on von Willebrand factor (VWF) pathophysiology who have tried for the last 20 years to improve clinical and laboratory assessments of this inherited bleeding disorder, VWD awareness remains poor not only at Low- (LIC) but also at Medium- (MIC) and High-Income Countries (HIC) because lab testing remains complex and costly. To determine the impact of these IGL into the current clinical and laboratory diagnosis of Italian VWD patients, we have recently conducted a survey among 43 Centers affiliated with Italian Association of Hemophilia Centers (AICE). Directors and Colleagues responsible for the management of VWD patients were invited to report in a detailed questionnaire how IGL diagnostic recommendations could be applied at their local sites. Results from such a survey showed that Bleeding Assessment Tools (BAT), VWF antigen (VWF:Ag), factor VIII pro-coagulant (FVIII:C) are currently in use in all Centers. The automatic assays for platelet-dependent VWF activity (PD-VWFact) with or without Ristocetin described in IGL have been used since 2021 in 37/43(86%) Centers. Among other lab tests, VWF collagen binding (VWF:CB), Ristocetin-Induced Platelet Agglutination (RIPA), multimeric analysis (VWF:MA), VWF propeptide (VWFpp), VWF:FVIII binding assay (VWF:FVIIIB) were available in 49%, 63%, 26%, 7% and 28% of AICE Centers, respectively. Analyses of VWF gene defects are available only at 3/43(7%) Centers. Desmopressin (DDAVP) infusion trial at diagnosis with measurements of VWF activities at 1 and 4 hours post-DDAVP is currently performed at 38/43(88%) Centers. Based on this information, a simplified clinical diagnosis using a few automatic tests before and after DDAVP has been proposed. This diagnostic approach will be validated prospectively in a large cohort of Italian VWD patients.

PO106

POST-SURGICAL BLEEDING IN UNKNOWN HETEROZYGOUS FACTOR XIII DEFICIENCY: A MONOCENTRIC CASE SERIES

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Background: Factor XIII deficiency is a rare bleeding disorder affecting the final stage of the coagulation, inherited in an autosomal recessive manner. Symptoms range from life-threatening hemorrhage to mild forms. Particularly, heterozygous carriers may show a bleeding tendency after traumatic injury or invasive procedures. The diagnosis of FXIII is challenging because standard coagulation tests are normal. However, FXIII deficiency has to be suspected in some situations and specific FXIII assays are required.
Aim: To describe a case series of patients presented with major post-surgical bleeding and unexpected mild factor XIII deficiency.
Methods: We included patients who required investigation due to major bleeding after surgery from February 2016 to April 2023. We collected the following data: sex, age, type of surgery, type of hemorrhage, timing of bleeding after intervention, treatment and FXIII levels during and after the acute event.
Results: Between 2016 to 2023, four patients referred to our Unit due to major post-surgical bleeding. Three patients were male and one was female with a median age of 45 years old. The first patient presented with a large spinal hematoma in anesthesia location, after knee surgery. He received blood transfusion and the surgical drainage of hematoma with worsening of bleeding. The second patient underwent to coronary by-pass complicated by bleeding in surgical site. A surgical revision was necessary with subsequently hemotorax. In the third patient kidney transplant was performed and severe bleeding with hypovolemic shock occurred. Surgical revision was necessary without stopping bleeding. The last patient underwent to glossectomy due to the cancer and received other two subsequently interventions because of bleeding on the surgical location. Bleeding occurred between 2 days and 14 days from surgery in all patients. Platelet count and standard coagulation assays were normal and nobody reported intraoperative complications. Thus, we performed FXIII subunit A assay with detection of low levels of FXIII in all patients (range between 39% to 6%, median value 18%). Everybody received infusions of plasmatic FXIII concentrates at 15-20 U/kg and monitored for FXIII levels to additional infusion (median 3 infusions) until resolution of hemorrhage. FXIII levels were measured again in all patients after several months from acute bleeding. In all patients a mild reduction of FXIII persisted with a median value of 48%. Another elective major surgery was subsequently planned in two of four patients. They were treated with FXIII concentrates infusion before and after surgery according to FXIII monitoring. No bleeding happened.
Conclusions: FXIII deficiency is a rare bleeding disorder that is not detected by standard coagulation assays. However, heterozygous FXIII deficiency should be suspected in some situations as in adult people with unexplained post-surgical bleeding. Detection of this condition requires a careful monitoring in high-risk bleeding situations as trauma or surgery. Multidisciplinary approach is recommended to select patients who benefit from the peri-operative treatment with FXIII concentrates and from the laboratory monitoring after surgery, in order to prevent bleeding.

PO107

LONG-TERM FOLLOW UP OF A CHALLENGING CASE OF CONGENITAL AFIBRINOGENEMIA AND RECURRENT VENOUS THROMBOEMBOLISM (VTE)

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Background: Congenital afibrinogenemia is associated with moderate to severe bleeding. The pharmacokinetic of fibrinogen after replacement therapy is variable among patients and it is important to adjust treatment individually. Thrombosis can also occur in 20% cases. When VTE occurs, anticoagulant treatment is challenging, as the basal prolongation of prothrombin time may affect INR monitoring limiting the use of vitamin K antagonists (VKA) for long term treatment. Due to the rarity of the disease, only anecdotal descriptions of treatment with DOACs are available.
Case Report: A 46 years old female patient, bw 50 Kg, affected from congenital afibrinogenemia, is on regular prophylaxis with fibrinogen concentrates since infancy due to initial bleeding phenotype (epistaxis and haematomas, then she had menorrhagia, haemoperitoneum and spontaneous haemothorax). In 2011, at age of 34, she presented a cerebral vein thrombosis with intracerebral hemorrhage, for which she received unfractionated heparin followed by long term coumarins with cumbersome monitoring of INR to maintain the 2-3 range. For difficult venous access a port-a-cath was inserted. In 2012 she suffered from left internal jugular vein thrombosis, and in 2014 from right internal jugular vein thrombosis, therefore anticoagulation was shifted from VKA to the anti-factor Xa inhibitor rivaroxaban. No VTE recurrence occurred for 6 years. In May 2020, during rivaroxaban treatment, she presented a distal and proximal deep vein thrombosis of the left leg, so rivaroxaban was stopped in favor of enoxaparin 4000 IU bid for six months and then anti-factor II inhibitor dabigatran 110 mg bid. In parallel, replacement treatment with 2 gr of fibrinogen concentrates was given daily in the first month of heparin anticoagulation, then it was continued two times per week. In 2021 a CT scan showed superior vena cava thrombosis and persistence of the right jugular vein thrombosis, a filiform left jugular vein and subclavian thrombosis. A progressive dyspepsia required a first temporary stop of dabigatran, substituted for few weeks by low molecular weight heparin (LMWH). In the meantime the patient asked for less frequent fibrinogen infusions, therefore the interval was prolonged from 3 to 4-7 days, obtaining to maintain a trough level of fibrinogen above 50 mg/dl, as suggested by consensus indications (Casini *et al.,* Haemophilia 2016). Resolution of dyspepsia was unfortunately only temporary, restarting with dabigatran reassumption, so in august 2023 it was substituted with apixaban 2.5 mg bid, with no more gastric symptoms. To date, the patient has no spontaneous bleeding manifestations nor thrombotic recurrences.
Conclusions: Our patient did not suffer from hemorrhages during treatment with DOACs plus regular replacement therapy with fibrinogen concentrates, with a satisfactory safety outcome. The high level of free thrombin available in afibrinogenemic plasma may be a rationale for use of dabigatran, if tolerated. In our case, rivaroxaban treatment proved to be safe and effective for a long period of time as well as apixaban is currently performing well in preventing recurrences in this rare condition. These data are encouraging for the use of DOACs in such a particular setting, however it is advisable to check periodically the plasma levels of anticoagulation by DOAC dosing.

PO108

COVID-19 INFECTION: AN INDEPENDENT HYPERCOAGULABLE STATE

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Background and Aims: A hypercoagulable state has been observed in patients with Covid-19 infection. This condition may lead to arterial and venous thrombosis. What has not been clarified is to investigate whether one or more clinical and laboratory variables can sustain hypercoagulability. This study aimed to detect hypercoagulability in a group of patients with Covid-19 infection by means of Clot Waveform Analysis (CWA) and the Endogenous Thrombin Potential ratio (ETPr). The former is referred to the detection of the dynamic of clot formation in aPTT test. CWA provides information on clot formation's velocity (1st derivative) and acceleration (2nd derivative). The latter, quantifies how much is the thrombin generation with and without Thrombomodulin. Both tests, therefore, may be complementary in the study of prothrombotic conditions as those studied here.
Methods: A total of 65 patients (44 men and 21 women, median age 67 years, range 27-93 years) and a group of 42 healthy subjects (19 men and 23 women, median age 59 years, range 22-73 years) were studied. aPTT ratio, CWA, Fibrinogen, D-Dimer and von Willebrand Factor (vWF) Antigen (vWF:Ag) and Ristocetin Cofactor (vWF:RiCo) were detected with an automatic coagulometer (ACL Top 550, Werfen, Milan, Italy). ETPr was measured by a Calibrated Automated Thrombogram (CAT) method (Thrombinoscope BV, Diagnostica Stago, Asnières sur Seine France) using the reagent PPP-Reagent with and without Thrombomodulin (+ / − TM). The Systemic Immune Inflammation Index (SII) along with several other variables (Lung Score, Hypertension,

Obesity, Diabetes, Glomerular Filtration Rate (GFR), Interleukin-6, Non Invasive Ventilation (NIV), Continuos Positive Airway pressure (CPAP), Colchicine and Remdesevir were also recorded. Data are presented as median and range. Mann-Whitney test and multivariate logistic regression were used for the statistical analysis (MedCalc, Ostend, Belgium).
Results: All the coagulative parameters were significantly different from those of healthy subjects (Table 1). No variable was found to be significantly associated with both CWA and ETPr, which were considered as dependent variables.
Conclusions: We detect a hypercoagulable state employing several coagulative parameters confirming previous **Results:** However, our data highlighted that hypercoagulability is independently present from other clinical and laboratory variables. In particular, the SII, a global index of systemic inflammation, was not different between patients with high, normal derivatives and ETPr. In other words, it seems that the Covid-19 infection can induce *per se* a hypercoagulable state. The primary findings presented in this abstract are based on Dr. Maria Filomena Ruberto's dissertation for the II-Level Master's Degree in Hemostasis and Thrombosis, which she received from the Catholic University in Rome, Italy, in conjunction with the Società Italiana per lo Studio dell'Emostasi e Trombosi (SISET), in November 2023.

Table 1.

Parameters (Median, range)	Covid-19 n=65	Healthy Controls n=42	p
aPTT ratio	0.95, 0.71-2.08	1.00, 0.84-1.25	0.0633
1st der aPTT (mAbs/s)	304.3, 162.4-551.0	224.2, 137.3-359.5	<0.0001
2nd der aPTT (mAbs/s²)	1069.4, 233.5-1925.6	788.15, 458.1-1233.8	<0.0001
Fibrinogen (mg/dL)	320.0, 177.0-523.0	247.5, 183.0-346.0	<0.0001
D-Dimer (ng/mL)	700.0, 101.0-75342.0	277.5, 5.0- 493.0	<0.0001
vWF:Ag (%)	477.6, 226.8-1091.5	137.8, 63.2-252.7	<0.0001
vWF:RiCo (%)	342.8, 122.8-595.7	104.45, 29.6-156.9	<0.0001
ETP ratio	0.70, 0.12-1.04	0.56, 0.32-0.90	0.0006
SII	1182.50, 69.00-27720.00	394.56, 154.72-1009.07	0.0005

Mann-Withney test. Data are expressed as median and range.

PO109

NON-INVASIVE VENTILATION SUPPORT DURING HOSPITALIZATION FOR SARS-COV-2 AND THE RISK OF VENOUS THROMBOEMBOLISM

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Background and Objectives: Despite SARS-CoV-2 infection represents a significant risk factor for venous thromboembolism (VTE), data on the impact of the use of non-invasive ventilation support (NIVS) on the risk of VTE during hospitalization are scarce.
Methods: Data of 1471 SARS-CoV-2 patients, hospitalized in a single hub during the first pandemic wave, were collected from clinical records including symptom type and duration, extension of lung abnormalities on chest computed tomography (CT), laboratory parameters and the use of NI*VS*. VTE occurrence during hospital stay was the main endpoint.
Results: Patients with VTE (1.8%) had an increased prevalence of obesity (26% *vs* 11%), diabetes (41% *vs.* 21%), higher CHA2DS2VASC score (4, IQR 2-5 *vs* 3, IQR 1-4, age- and sex-adjusted p=0.021), cough (65% *vs* 44%) and experienced significantly higher rates of NI*VS* (44% *vs* 8%). On a stepwise multivariate logistic regression model, the prevalence of electrocardiogram abnormalities (Odds Ratio (OR) 2.722, 95% confidence interval (CI) 1.039–7.133, p=0.042), cough (OR 3.019, 95% CI 1.265–7.202, p=0.013) CHA2DS2-VASC score >3 (OR 3.404, 95% CI 1.362–8.513, p =0.009) and the use of NI*VS* (OR 15.530, 95% CI 6.244–38.627, p<0.001) were independently associated with the risk of VTE during hospitalization. NI*VS* remained an independent risk factor for VTE even after adjustment for the period of admission within the pandemic wave.
Conclusions: Our study suggests that NI*VS* a risk factor for VTE during hospitalization in SARS-CoV-2 patients. Future studies should assess the optimal prophylactic strategy against VTE in patients with SARS-CoV-2 infection.

PO110

THE ROLE OF RITUXIMAB IN A YOUNG WOMAN WITH ACQUIRED HEMOPHILIA A AND RECENT RECURRENCE OF THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background: Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy caused by deficiency of ADAMTS13: a plasma protease that cleaves high molecular weight von Willebrand factor. Acquired hemophilia A (AHA) is a rare bleeding disorder characterized by the formation of anti-factor VIII (FVIII) antibodies. We describe the case of a patient with relapsing TTP and recent diagnosis of AHA, successfully treated with rituximab.
Case Report: A 55-year-old woman was diagnosed with AHA in December 2023, during treatment with steroids, started some months before and continued at a progressively reduced dose for a recent relapse of TTP (first episode in 2018). Family history was negative for hemorrhagic disorders. There was a history of arterial hypertension and hypercholesterolemia, and a previous breast cancer in 2013, treated with hormonal therapy for 5 years and radiotherapy, as well as an episode of DVT of lower limb in 2018, followed by, a few months later, the first episode of TTP. The physical examination showed a large muscular hematoma of the left thigh with dislocation of the femoral vessels and compression of the femoral vein. Large hematomas of the arms were also evident. Laboratory tests on admission showed severe

anemia (Hb 7.3 g/dL), treated with blood transfusions as needed. FVIII:C levels on admission were 2%, with an inhibitor titre of 14 Bethesda Units. Activated recombinant factor VII concentrate (rFVIIa) 90 µg/kg i.v. every 4-6 hours for a total of 5 days, was administered. The dose of prednisone was increased to 1mg/kg/day. After approximately one week, a decreased FVIII:C (0.6%) was found. As there was no significant response to steroid after 4 weeks, and as vertebral collapse was found at the L2 level, rituximab (375 mg/m2) was administered weekly, at the same time as the dose of prednisone was decreased to 50 mg per day. After the second rituximab infusion, prednisone was further reduced to 35 mg, with subsequent therapeutic response. Oncological recurrence was excluded.

Conclusions: TTP and AHA represent two rare pathologies, the first with an incidence of 3-13 cases per million per year and the second with an incidence of 1-4 cases per million per year. The peculiarity of the case described is the appearance of AHA in a patient with recent relapse of TTP and still undergoing tapering steroid treatment. Although the possible correlation between AHA and autoimmune diseases (SLE, RA, polymyalgia rheumatica) is known, the correlation between AHA and PTT is rarely described. At the basis of this, as in the clinical case described, there would seem to be an exacerbation of the pre-existing immune dysregulation (relapse of PTT, in the specific case), which ultimately may have led to the clonal selection of B cells capable of producing specific autoantibodies, including those against FVIII. The real challenge for the clinician is represented not only by the early diagnosis of two diseases that are still poorly diagnosed today, but above all by the need for timely and effective treatment. Rituximab offers an additional option for those who do not respond to conventional treatment, as in the case of our steroid-refractory patient, or for those who have multiple relapses. For both pathologies, this second-line treatment not only promotes disease remission but also reduces the relapse rate, improving the patient's quality of life.

PO111

RELATIONSHIP BETWEEN PLASMA SUPAR LEVELS AND THE INCIDENCE OF THROMBOEMBOLIC EVENTS AND MORTALITY IN A COHORT OF HOSPITALIZED PATIENTS WITH ACUTE RESPIRATORY FAILURE SECONDARY TO SARS-COV2 PNEUMONIA

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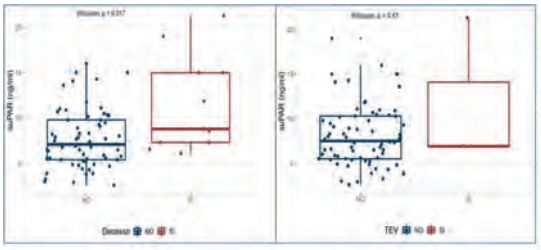
Background: Venous thromboembolism (VTE) plays an important role in contributing to mortality and morbidity in COVID-19 (Poor 2021). The levels of the soluble urokinase-type plasminogen activator receptor (suPAR) reflect hyperinflammation and are strongly predictive of outcomes in COVID-19 (Rovina et al 2020). There is unclear association between suPAR and VTE.

Purpose of the study: The primary endpoint of the study was the verification of a correlation in a cohort of patients hospitalized for COVID-19 between plasma levels of suPAR and the incidence of VTE. The secondary endpoints were the verification of the correlation between suPAR and mortality and the correlation between suPAR and D-Dimer and between suPAR and IL-6.

Materials and Methods: This is a single-center retrospective observational study performed on a cohort of 76 patients (median age 66 years, males 63.2%) hospitalized for COVID-19 from March 2021 to June 2022.

Results: regarding the primary endpoint, the median of suPAR levels in patients presenting with VTE is 6.90 ng/mL (IQ Q1-Q3 6.90 - 18.90ng/mL), the median of suPAR in patients without VTE is 7.50ng/mL (IQ Q1-Q3 5.47 - 10.30ng/mL). The p value associated with the Wilcoxon test is not significant (p=0.47). Regarding the secondary endpoint, the median of the suPAR levels is 8.80ng/mL (IQ Q1-Q3 7.31 - 15.00ng/mL) in the deceased patients, the median of the suPAR levels in the surviving patients is 7.10ng/mL (IQ Q1-Q3 5.40 - 9.93ng/mL). The p value associated with the Wilcoxon test is significant (p=0.017). The correlation between suPAR and D-Dimer was low (Spearman correlation index ρ=0.42) and the correlation between suPAR and IL-6 was very low (ρ=0.024) (Figure 1).

Conclusions: There was no statistically significant association between suPAR and VTE in this study. On the other hand, a significant association was found between suPAR and mortality.



Association between suPAR (ng/mL) and mortality and between suPAR and venous thromboembolic events (VTE).
Data expressed as median and interquartile range (IQR): Median [Q1 - Q3], p value associated with Wilcoxon test

Figure 1.

PO112

HIGH PLASMA C5A AND C5B-9 LEVELS DURING QUIESCENT PHASES ARE ASSOCIATED WITH SEVERE ANTIPHOSPHOLIPID SYNDROME SUBSETS

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Background and Aims: Complement activation have recently emerged as an important factor in the pathogenesis of antiphospholipid syndrome (APS) - related clinical events. High plasma C5a and C5b-9 levels are considered a sign of complement activation. In the attempt to explore new biomarkers of APS disease activity to guide clinical judgment and to personalize APS treatment we evaluate the association of C5a and C5b-9 plasma levels with different clinical and laboratory APS subsets.
Patients and Methods: We conducted a monocentric exploratory cross-sectional study. Plasmas of 62 quiescent APS patients, 40 with thrombosis responsive to anti-vitamin K (VKA) therapy (TAPS), 13 with refractory to VKA recurrent thrombosis (RAPS), 9 with CAPS, 13 active APS (2 TAPS, 7 RAPS, and 4 CAPS), and 38 healthy controls (HC) sex and age-matched were recruited. Plasma concentrations of C5a and C5b-9 were assessed using commercial ELISA assays.
Results: The C5b-9 levels in quiescent CAPS were significantly higher than in TAPS [median, 330.2 ng/mL (IQR, 86.6); *vs* 189.7 ng/mL (IQR, 138.9) and in HC [median, 330.2 ng/mL (IQR, 86.6) *vs* 120.9 ng/mL (IQR, 83.7)]. Similarly, the C5a levels were significantly higher in CAPS than in TAPS [median, 27.6 ng/mL (IQR, 58.4) *vs.* 8.9 ng/mL (IQR, 8.3) and the HC [median, 27.6 ng/mL (IQR, 58.4) *vs.* 4.9 ng/mL (IQR, 4.9)]. Moreover, both C5a and/or C5b-9 were significantly higher in RAPS than in TAPS [median 15.6 ng/mL (IQR, 51.8) *vs.* 11.6 ng/mL (IQR, 9.3) and median 814.6 ng/mL (IQR, 2808.4) *vs.* 309.6 (291.7)]. In addition, C5a and/or C5b-9 significantly prevailed in the patients with active APS *vs.* Quiescent APS [median 41.2 ng/mL (IQR, 67.3) *vs.* 14.3 ng/mL (IQR, 8.3) and median 1691.0 ng/mL (IQR,1788.3) *vs.* 448.9 ng/mL (IQR, 463.6)] as well as in the small-vessel thrombosis (p=0.0088), just as C5b-9 did in the triple antiphospholipid antibody-positive patients (p=0.0248). The ROC curve showed that the best cut-offs for C5a and C5b-9 levels had a higher sensitivity, specificity, and likelihood ratio in the CAPS and RAPS groups than in the TAPS subset.
Conclusions: Persistent, high plasma C5b-9 and C5a levels during quiescent phases identify APS patients with more severe disease who may develop recurrent thrombosis and benefit from complement inhibition treatment during an acute disease phase.

PO113

COMPARISON BETWEEN LABORATORY PARAMETERS OF PATIENTS ADMITTED WITH CORONAVIRUS DISEASE 2019 (COVID-19) DURING DIFFERENT PANDEMIC WAVES

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Background and Aims: Coronavirus disease 2019 (COVID-19) has long been associated with heterogeneously altered laboratory findings, and in particular a peculiar coagulopathy characterized by thrombocytopenia, elevated D-dimer and marked hypercoagulable profile on thromboelastometry, resulting in increased risk of venous thromboembolism. As several new variants emerged, each with different clinical and laboratory characteristics, we endeavoured to compare laboratory findings of patients admitted with acute COVID-19 across variants.
Methods: All consecutive adult patients admitted with acute COVID-19, confirmed by positive nasopharyngeal swab, to Internal Medicine Departments of Padova University Hospital divided into four different groups: (G1) 19th March 2020-31st December 2020: I and II waves; (G2) 10th March 2021-18th April 2021: III wave; (G3) 18th January 2022-30th November 2022: IV, V and VI waves; and (G4) 13th September 2023-24th January 2024: IX wave. We retrieved demographic, clinical, and laboratory data from electronic medical records and compared G1 *vs.* G2, G3, G4.
Results: We enrolled n. 328 patients (median age 80 yrs; M/F 52.2/47.8%): n. 155 in G1, n. 79 in G2, n. 40 in G3 and n. 54 in G4 (Table 1). No significant differences were observed according to age, whereas there was a significantly higher prevalence of females in G1 (p=.001). The WBC count was significantly higher in G1 *vs.* G2 (p<.001). Lymphocyte count was significantly lower in G1 *vs.* G3, G4 (p<=.05). Significantly higher haemoglobin was recorded in G1 *vs.* G3 (p<.001). Significantly higher platelet count was found in G1 *vs.* G2, G3 (p=.001). No significant differences were observed in creatinine, international normalized ratio (INR), partial thromboplastin (aPTT) and D-dimer. PCR and PCT were significantly higher in G1 *vs.* G2, G3 (p<.001). We also observed higher fibrinogen and antithrombin in G1 *vs.* G2, G3 (p<.001). Significantly higher vWF levels were recorded in G1 *vs.* G2, G3, G4 (p<.001).

Table 1.

	Total (n = 328)	I-II waves (n = 155)	III wave (n = 79)	IV-V-VI waves (n = 40)	IX wave (n =54)
Age, yrs	80 (70-86)	78 (67-85)	79 (67-86)	84 (77-87)	81 (76-87)
Sex, n (%)					
Female	157 (47.8%)	80 (51.6%)	41 (51.9%)	22 (55.0%)	14 (25.9%)
Male	171 (52.2%)	75 (48.4%)	38 (48.1%)	18 (45.0%)	40 (74.1%)
WBC count, x10^9/L	6.48 (4.73-9.23)	6.99 (5.18-9.98)	5.89 (4.35-7.94)*	5.64 (3.30-7.65)	7.24 (4.71-9.22)
Lymphocyte count, x10^9/L	0.94 (0.63-1.22)	0.91 (0.64-1.21)	0.8 (0.56-1.08)	1.1 (0.91-1.32)*	1.08 (0.65-1.65)*
Haemoglobin, g/L	124 (109-137)	126 (112-136)	128 (115-140)	118 (104-125)*	118 (107-135)
Platelet count, x10^9/L	207 (155-258)	219 (168-283)	201 (153-235)*	222 (200-251)	178 (125-227)*
Creatinine, umol/L	80 (66-108)	89 (71-117)	73 (61-89)	77 (58-83)	94 (64-120)
INR	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.1-1.1)	1.2 (1.1-1.2)	1.2 (1.1-1.3)
aPTT ratio	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.0)	1.1 (1.0-1.1)	1.1 (1.0-1.3)
D-dimer, ng/L	347 (150-921)	288 (165-574)	254 (150-419)	604 (195-1024)	939 (150-1673)
PCR, mg/L	68 (29-119)	82 (41-120)	62 (26-105)*	49 (40-79)*	73 (20-120)
PCT, ng/mL	0.14 (0.05-0.48)	0.15 (0.05-0.67)	0.08 (0.04-0.23)*	0.15 (0.10-0.29)*	0.18 (0.04-1.30)
Fibrinogen, g/L	4.7 (4.0-5.3)	5.0 (4.3-5.0)	4.7 (4.2-5.2)	4.7 (4.2-5.0)*	4.1 (3.4-4.8)*
Antithrombin, %	90 (83-98)	93 (85-102)	91 (85-102)	85 (82-87)*	85 (83-88)*
vWF, %	262 (229-361)	343 (244-407)	235 (216-247)*	262 (224-274)*	284 (218-287)*

Conclusions: Our study revealed a heterogeneous and peculiar laboratory profile in patients admitted with acute COVID-19 across pandemic waves. G1 patients were at higher risk of developing severe COVID-19. Larger

prospective studies are needed to ascertain the determinants of laboratory findings in each pandemic wave.

PO114

RETROSPECTIVE COHORT STUDY COMPARING THE CLINICAL PROFILES AND OUTCOMES OF PATIENTS ADMITTED WITH CORONAVIRUS DISEASE 2019 (COVID-19) DURING DIFFERENT PANDEMIC WAVES

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Background and Aims: Several pandemic waves caused by different variants of Coronavirus disease 2019 (COVID-19) have been recorded worldwide. It remains uncertain how patients' clinical profiles and outcomes were impacted by each pandemic wave. Therefore, we conducted a retrospective cohort study aiming to compare the clinical profiles and outcomes of patients admitted with acute COVID-19 to the Internal Medicine Departments of Padova University Hospital across variants.

Methods: We enrolled all consecutive adult patients with a confirmed diagnosis of acute COVID-19 via nasopharyngeal swab, admitted to Internal Medicine Departments of Padova University Hospital. Patients were divided into four different groups: (G1) 19th March 2020-31st December 2020: I and II waves; (G2) 10th March 2021-18th April 2021: III wave; (G3) 18th January 2022-30th November 2022: IV, V and VI waves; and finally (G4) 13th September 2023-24th January 2024: IX wave. Demographic and clinical characteristics, and outcomes were retrieved from electronic medical records and we compared G1 *vs.* G2, G3, G4. The outcomes examined were: incidence of symptomatic venous thromboembolism (VTE), acute coronary syndrome (ACS), stroke/transient ischemic attack (TIA), respiratory failure, acute kidney insufficiency (AKI), sepsis, septic shock, length of hospital stay (LOHS), clinically relevant hemorrhage and 28-day mortality.

Results: We enrolled n. 344 patients (median age 80 yrs; M/F 52.1/47.9%): n. 155 in G1, n. 79 in G2, n. 50 in G3 and n. 60 in G4 (Table 1). We observed no significant differences according to age, whereas a significantly higher prevalence of females was observed in G1 *vs.* G4 (p=.001). Septic shock was significantly more prevalent in G1 *vs.* G2, G3, G4 (p <.001) in each comparison. The prevalence of respiratory failure was significantly higher in G1 *vs.* G4 (p=.02). VTEs were significantly higher in G1 *vs.* G3, G4 (p=.04 in each comparison). No significant differences were observed in ACS, stroke/TIA, LOHS and clinically relevant hemorrhage. Finally, 28-day mortality was significantly higher in G1 *vs.* G3, G4 (p=.03 and <.001, respectively).

Conclusions: Our study revealed dynamic trends in patient outcomes across pandemic waves. Patients in G1 and G2 were at higher risk of developing a severe form of COVID-19 and poor outcomes. Larger prospective studies are needed to better understand the determinants of and the risk factors associated with clinical outcomes in each pandemic wave.

Table 1.

	Total (n = 344)	I-II waves (n = 155)	III wave (n = 79)	IV-V-VI waves (n = 50)	IX wave (n = 60)
Age, yrs	80 (70-86)	78 (67-85)	79 (67-86)	84 (77-87)	81 (76-87)
Sex					
Female	165 (47.9)	80 (51.6)	41 (51.9)	27 (54.0)	17 (28.3)
Male	179 (52.1)	75 (48.4)	38 (48.1)	23 (46.0)	43 (71.7)
Sepsis	33 (9.6)	20 (12.9)	5 (6.3)	2 (4.0)	6 (10.0)
Septic shock	17 (4.9)	15 (9.7)	2 (2.5)*	0 (0)*	0 (0)*
Respiratory failure	51 (14.8)	27 (17.4)	16 (20.3)	5 (10.0)	3 (5.0)*
AKI	20 (5.8)	13 (8.4)	2 (2.5)	2 (4.0)	3 (5.0)
VTE	50 (14.5)	28 (18.1)	15 (19.0)	3 (6.0)*	4 (6.7)*
VTE in Pneumoniae	46/222 (20.7)	24/120 (20.0)	15/64 (23.4)	3/16 (18.8)	4/22 (18.2)
ACS	14 (4.1)	7 (4.5)	3 (3.8)	1 (2.0)	3 (5.0)
Stroke/TIA	5 (1.4)	4 (2.6)	1 (1.3)	0 (0)	0 (0)
LOHS, days	9 (6-14)	10 (6-16)	10 (6-14)	9 (6-14)	6 (4-8)
Haemorrhage CRL	11 (3.2)	5 (3.2)	3 (3.8)	1 (2.0)	2 (3.3)
Death	39 (11.3)	24 (15.5)	12 (15.2)	2 (4.0)*	1 (1.7)*

PO115

ROTATIONAL THROMBOELASTOMETRY (ROTEM®) AND PLATELET AGGREGOMETRY (MULTIPLATE®) IN PATIENTS ADMITTED WITH ACUTE CORONAVIRUS DISEASE 2019 (COVID-19) DURING DIFFERENT PANDEMIC WAVES

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Background and Aims: Patients hospitalized with acute Coronavirus disease 2019 (COVID-19) have been reported to be particularly prone to develop thrombotic events. Several pathogenetic mechanisms have been proposed to explain the correlation between the acute infection and the persistent prothrombotic state. In particular, the cytokine storm observed in patients with acute COVID-19 promotes a hypercoagulable state via three main mechanisms: endothelial damage, activation of coagulation and platelets, and suppression of fibrinolysis. Traditional coagulation tests are limited in their ability to characterize COVID-19-associated hypercoagulability. Therefore, we conducted a retrospective cohort study aiming to compare the rotational thromboelastometry and platelet aggregometry profiles of patients admitted with acute COVID-19 infection to Internal Medicine Departments of Padova University Hospital infected with different variants.

Methods: We enrolled all consecutive adult patients with acute COVID-19, confirmed by positive nasopharyngeal swab, admitted to Internal Medicine Departments of Padova University Hospital divided in four different groups: (G1) 19th March 2020-31st December 2020: I and II waves; (G2) 10th March 2021-18th April 2021: III wave; (G3) 18th January 2022-30th November 2022: IV, V and VI waves; and (G4) 13th September 2023-24th January 2024: IX wave. Demographic, clinical and

thromboelastometry/aggregometry data were retrieved from electronic medical records and we compared G1 *vs.* G2, G3, G4. The ROTEM® assays INTEM (to assess intrinsic coagulation pathway), EXTEM (to assess the extrinsic coagulation pathway) and FIBTEM (to assess fibrinogen contribution to clot formation and stability) were used to measure the following parameters: I) clotting time (CT, sec), the time from the beginning of the coagulation analysis until an increase in amplitude of 2 mm; II) clot formation time (CFT, sec), the time between an increase in amplitude of the thromboelastogram from 2 to 20 mm; III) maximum clot firmness (MCF, mm), the maximum amplitude reached in the thromboelastogram. Aggregometry was tested using the Multiplate function analyzer. The instrument measures the impedance between two copper wires. Platelet aggregation was expressed as units of area under the curve (AUC).

Results: We enrolled n. 328 patients (median age 80 yrs; F/M 47.8/52.2%): n. 155 in G1, n. 79 in G2, n. 40 in G3 and n. 54 in G4 (Table 1). We found no significant differences according to age, whereas a significantly higher prevalence of females was observed in the G1 *vs.* G4 (p=.001); CT in INTEM and EXTEM were significantly shorter in G1 *vs.* G4 (p<.001 in both comparisons); CFT in EXTEM was significantly shorted in G1 *vs.* G2, G3, G4 (p<.001 in each comparison); MCF in EXTEM was significantly higher in G1 *vs.* G2, G3, G4 (p<.001 in each comparison); MCF in FIBTEM was significantly higher in G1 *vs.* G3, G4 (p<.001 in each comparison). No significant differences were observed in platelet aggregometry parameters.

Conclusions: We observed a heterogeneous and peculiar whole blood laboratory profile, via thromboelastometry and aggregometry assays, in patients admitted with acute COVID-19 across pandemic waves. Notably, G1 patients were at higher risk of developing a hypercoagulable profile and thus more severe COVID-19. Larger prospective studies are needed to better understand the determinants of whole blood laboratory alterations associated with each pandemic wave.

Table 1.

	Total (n = 328)	I-II waves (n = 155)	III wave (n = 79)	IV-V-VI waves (n = 40)	IX wave (n =54)
Age, yrs	80 (70-86)	78 (67-85)	79 (67-86)	84 (77-87)	81 (76-87)
Sex, n (%)					
Female	157 (47.8%)	80 (51.6%)	41 (51.9%)	22 (55.0%)	14 (25.9%)
Male	171 (52.2%)	75 (48.4%)	38 (48.1%)	18 (45.0%)	40 (74.1%)
Clotting time, sec					
INTEM	186 (172-205)	184 (171-200)	185 (168-199)	185 (172-192)	205(175-242)*
EXTEM	74 (66-85)	71 (64-81)	74 (66-83)*	79 (68-86)	79 (70-92)*
Clot formation time,sec					
INTEM	58 (49-72)	51 (45-64)	67 (55-86)	63 (52-70)	65 (54-88)
EXTEM	60 (49-75)	52 (43-63)	71 (57-86)*	62 (60-67)*	65 (54-84)*
Maximum Clot Firmness, mm					
INTEM	66 (62-71)	68 (63-72)	65 (60-68)	67 (65-69)	64 (58-67)
EXTEM	69 (64-73)	71 (66-74)	66 (61-70)*	68 (65-70)*	67 (59-70)*
FIBTEM	29 (24-35)	31 (26-37)	29 (24-37)	24 (22-29)*	24 (20-31)*
MULTIPLATE, AUC					
ASPI TEST	47 (28-68)	49 (26-72)	46 (25-73)	48 (36-64)	41 (30-51)
ADP TEST	57 (40-76)	59 (37-79)	62 (48-85)	52 (32-69)	54 (45-62)
TRAP TEST	93 (73-117)	95 (73-118)	98 (71-124)	83 (65-99)	87 (78-107)

PO116

ROLE OF INFLAMMATION AND SARS-COV-2 RNAEMIA IN PLATELET DYSFUNCTION IN COVID-19 PATIENTS

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Background and Aims: COVID-19 has been associated with a high rate of thrombotic and bleeding complications. This may be due, at least in part, to the presence of both activated and degranulated platelets, though the underlying mechanisms are not fully understood. Emerging hypotheses are a direct interaction between SARS-CoV-2 and platelets, alongside an inflammatory response driven by circulating chemokines and cytokines capable of activating platelets. The aim of our study was to evaluate the role of SARS-CoV-2 RNAemia and of the milieu of peripheral chemokines and cytokines on platelet dysfunction during acute SARS-CoV-2 infection.

Methods: Patients with confirmed SARS-CoV-2 infection were included between March 2021 and August 2022, exhibiting varying degrees of clinical severity, from mild to severe symptoms, including pneumonia. Platelet dysfunction was defined based on the content of platelet δ-granules, measured by the firefly luciferin/luciferase method in a lumiaggregometer. Platelet-monocyte aggregates (PMA) were measured in citrated whole blood stained with fluorescein isothiocyanate-conjugated anti-human CD14 and allophycocyanin-conjugated anti-human CD41a and analysed by flow cytometry. Plasmatic SARS-CoV-2 RNA was assessed by real-time Polymerase Chain Reaction (PCR), and plasmatic chemokines and cytokines were quantified by flow cytometry using cytometric bead array.

Results: A total of 75 patients were enrolled in the study and stratified into two groups based on their platelet δ-granule content. Of the 75 patients, 57 were classified as having normal δ-granule content ($COV_{\delta\text{-norm}}$: ADP >1.98 nmol/10^8 platelets and ATP/ADP <3.47 ratio) and 18 as having low platelet δ-granule content ($COV_{\delta\text{-low}}$: ADP <1.98 nmol/10^8 platelets and ATP/ADP >3.47 ratio) (Figure 1A). The groups were comparable in terms of age and comorbidities. The study did not reveal a significant difference in SARS-CoV-2 RNAemia between the two groups (3.374 *vs* 3.319 RNA log10 copies/mL, p= 0.9755). However, the $COV_{\delta\text{-low}}$ group exhibited markedly higher levels of several key inflammatory mediators, including GM-CSF, IFN-γ, TNF-α, IL-4, IL-5, IL-6, IL-10, IL-12 and IL-17A (Figure 1B), suggesting a potent inflammatory response associated with platelet dysfunction. Similar results, albeit less pronounced, were observed when patients were classified based on their platelet activation phenotype (not shown). To determine if platelet dysfunction manifested early in the course of acute SARS-CoV-2 infection, we stratified the study popula-

tion in 3 tertiles based on the time from symptom onset to blood sampling. Interestingly, our findings revealed a progressive increase in the proportion of patients with degranulated platelets: 8% in the first 1-4 days, 18 between days 5 and 8 and 58% after day 8. Similar trends were observed for the peripheral cytokine milieu. In contrast, SARS-CoV-2 RNAemia notably decreased during the later stages of acute infection (Figure 1C).

Conclusions: Our data suggest that during acute SARS-CoV-2 infection, the peripheral chemokine and cytokine milieu plays a crucial in the onset of platelet dysfunction, which occurs mostly after 8 days since symptom onset. These findings underscore the importance of managing inflammation to mitigate thrombotic risks in COVID-19, proposing further research into targeted therapies that could modulate the inflammatory response to prevent platelet dysfunction in affected patients.

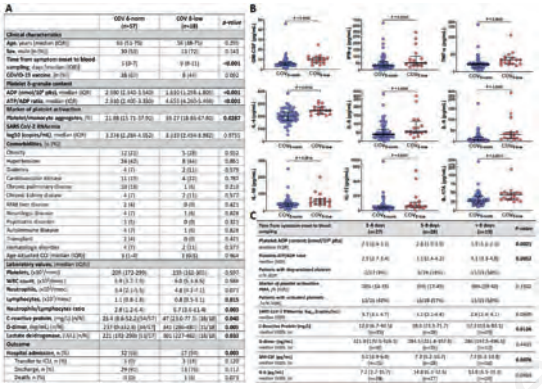

Figure 1.

PO117

POST THROMBOTIC SYNDROME: NEW INSIGHTS FROM AUTOIMMUNE DISEASES

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Background and Aims: It is well established that patients with detectable blood autoantibodies are at major risk of developing cardiovascular diseases and venous thrombosis, even when a clinically evident autoimmune disorder is not diagnosed. Our understanding of the complexity of thrombo-immune cross-talk is still limited but it has been hypothesized that dysregulated inflammatory response could affect both formation and resolution of vein thrombotic occlusion. The objective of this study is to investigate if the presence of autoantibodies is associated with post-thrombotic syndrome.

Methods: We enrolled 84 patients (aged 52-80 years old, 41 men) affected by lower limb deep vein thrombosis, including 26 patients with documented autoimmune disorders. To investigate the presence of post thrombotic syndrome, we performed both clinical evaluation (Villalta score) and venous color-doppler ultrasound at the end of the anticoagulation treatment, measuring the extension of residual thrombotic obstruction. Moreover, in the subgroup of 26 patients affected by autoimmune disorders, we investigated the presence of lupus anticoagulant (LAC) and antinuclear antibodies (ANA); than we measured inflammatory markers such as C-reactive protein (CRP) and erythrosedimentation velocity (VES).

Results: The analysis of post thrombotic syndrome included 84 patients, following provoked (n= 42) or unprovoked event (n= 42) and involving proximal (n= 52) or distal veins (n= 32). Sixty percent (60%) of patients without autoimmune disorders (n=58) had a residual thrombotic occlusion documented by color-doppler ultrasound and any of them (37%) had developed clinical signs with a Villalta score rated up to 5 points. In the subgroup of patients affected by autoimmune diseases we found 8 LAC positive tests, 13 patients with detectable ANA antibodies and 5 patients with both LAC positive test and ANA antibodies. Post thrombotic syndrome with a vein residual thrombotic obstruction was found in all patients with both LAC and ANA (n=5); in all patients with only ANA antibodies (n=8), and in one patient with only LAC positive test. No significant correlation was found between inflammatory markers and post thrombotic syndrome.

Conclusions: The post thrombotic syndrome is the most common complication of deep vein thrombosis, occurring in 20-50% of patients and causing a chronic and potentially disabling condition. Although there are several aspects that contribute to developing this syndrome, the pathophysiological mechanisms underlying this complication are not fully understood. Our results have highlighted that patients affected by autoimmune diseases, in particular the ANA group, develop more often severe post thrombotic syndrome due to residual thrombotic obstruction. It might suggest that autoantibodies could have a role in the balance of hemostatic system, affecting the resolution of the fibrin clot.

[These results were presented as thesis in "Haemostasis and Thrombosis Catholic University-SISET" Master Degree].

PO118

HOW GENETIC PROFILES CAN INFLUENCE PROGNOSIS OF COVID-19 PATIENTS: IDENTIFICATION OF DIFFERENT PATHOGENICITY GENETIC PROFILES BY HIGH-THROUGHPUT SEQUENCING

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Background: Since the 2019 SARS-CoV-2 pandemic outbreak, hundreds of studies reported evidences of a host genetic background's role in influencing both susceptibility to virus infection and the severity of the clinical pictures. Severe SARS-CoV-2 infections are often characterized by perturbation of physiological coagulation mechanisms, and are associated with a high incidence of thrombotic complications. In this study, genetic characterization of 80 COVID-19 patients referred to the Advanced Molecular Genetics Laboratory, Atherothrombotic Diseases Center, Careggi Hospital-University of Florence, was made by Next Generation Sequencing (NGS) in order to identify genetic profiles associated with the severity of the disease [death and admission in intensive care unit (ICU) *vs* early discharged patients] and thus potentially representing prognostic factors modulating the susceptibility to virus entry and complications (in particular thrombosis).
Methods: NGS was performed by Illumina MiSeq and Haloplex protocol targeting 7 virus entry-related genes (*ACE2, TMPRSS2, CTSL, CTSB, HSPA5, IL6, FURIN*) and 11 genes (*PROC, PROS1, FGA, FGB, FGG, SERPINC1, F2, F5, F10, PLAT, PLG*) known to be involved in the coagulation process.
Results: 42 heterozygous rare variants [Minor Allele Frequency (MAF)<0.01] were identified in 34/80 patients involving all 7 genes included in the virus entry-related panel. The most affected genes were *TMPRSS2* and *CTSB* (respectively 30% and 23% of total rare variants). No statistically significant differences were observed for these 7 genes between ICU *vs* early discharged patients. As regard the 11 coagulation genes panel, 69 rare variants have been identified at the heterozygous state in 50 of the 80 patients studied 28/40 ICU/dead patients (70%) *vs* 22/40 early discharged patients (55%): 28 missense, 20 synonymous, 11 non-deep intronic and 10 variants concerning zone 3'-5' UTR/downstream. Cumulatively, 45 out of 69 variants (65%) were observed in ICU (Intensive Care Unit hospitalization) or dead patients. In particular, 18 out of 69 variants (26,1%) were classified as VUS (Variant of Uncertain Significance), likely pathogenetic or pathogenic using the ACMG criteria, and 65% (12 out of 18) of these were observed in ICU/dead patients. Thirteen patients carried 2 or more rare variants: 69% (9/13) of these were ICU/dead patients, a percentage that becomes 100% when considering patients with at least 3 variants (3/3).
Conclusions: Our data suggest how genetic variants involving the host's virus entry machinery are not likely to exert a significant effect in modulating the severity of the COVID-19 progression. On the other hand, NGS results regarding the coagulation panel show that genetic variability, due to rare variants, might modulate clinical severity of COVID-19 disease in patients, when considering the prognosis parameters of death, intensive care unit hospitalization and early discharge from the hospital.

PO119

PLATELET ACTIVATION IN BRONCHIAL ASTHMA ACCORDING TO ASTHMA ENDOTYPE AND CLINICAL SEVERITY

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Background: Asthma is a chronic inflammatory disease in which different endotypes have been identified: type 2, allergic and/or eosinophilic, the most frequent and non-type 2, neutrophilic or paucigranulocytic, with late onset and more correlated with risk factors such as smoking, pollution and obesity. In addition to the role of platelets in hemostasis and thrombosis, there is a growing interest in their immunological function and in their role in the pathogenesis of asthma. Activated platelets produce soluble factors and directly interact with immune cells, thereby promoting an inflammatory phenotype. Furthermore, platelets participate in tissue injury and promote abnormal tissue healing, leading to fibrosis.
Objectives: Our aim was to assess whether platelets are activated in asthma patients, and to establish the extent of platelet activation, as reflected by surface expression of markers such as p-selectin and CD40, according to asthma endotype and severity.
Methods: In a prospective observational study, we enrolled twenty-nine patients (mean age 45.08 ±17.37) with different stages (3, 4, 5) of bronchial asthma severity. We also classified bronchial asthma patients according to the inflammatory endotype: type 2, allergic (GT2A, n=13) and non-allergic (GT2NA, n=7) and non-type 2 (GNT2, n=4). Patients were evaluated with clinical assessment and analysis of markers of platelet activation (CD40L and P-selectin expression on platelet surface by flow-cytometry).
Results: Step 5 asthma patients had a higher percentage (%CD61+/CD62p+: step 3+4 *vs* stage 5, p=0.030; Figure 1A) and a trend for higher mean flow intensity of p-Selectin-expression on platelets (MFICD61+/CD62p+: step 3+4 *vs* stage 5, p=0.068; Figure 1C) as compared to stage 3 and 4. No differences were observed for CD40 platelet expression (Figure 1B, 1D). Within patients with GT2A endotype, we confirmed an increased percentage of p-Selectin-positive platelets in step 5 *vs*- step 3+4 (%CD61+/CD62p+: step 3+4 *vs* step 5, p=0.030; Figure 2A) and a trend for a higher percentage of CD40-positive platelets (%CD61+/CD40+: step 3+4 *vs* stage 5, p=0.073; MFICD61+/CD40+ Figure 2B; step 3+4 *vs* stage 5,

p=0.051; Figure 2D). Analysis by endotype showed reduced levels of platelet activation in the GNT2 group as compared to the other groups (%CD61+/CD62p+: GT2A *vs* GNT2, p=0.003; GT2NA *vs* GNT2, p=0.006; Figure 3A) (MFICD61+/CD62p+: GT2NA *vs* GNT2, p=0.042; Figure 3C). No differences were observed for platelet CD40 surface expression according to asthma phenotype (Figure 3B, 3D).

Conclusions: Overall, our study demonstrated that type 2 asthma endotype is characterized by platelet activation, and that platelets from severe-stage allergic patients have an hyper-reactive state, despite the wider use of ant inflammatory agents in step 5. Larger scale studies are needed to better characterize the role of activated platelets in the pathogenesis of allergic asthma and to identify platelet-derived biomarkers of response to established or novel therapeutic strategies.

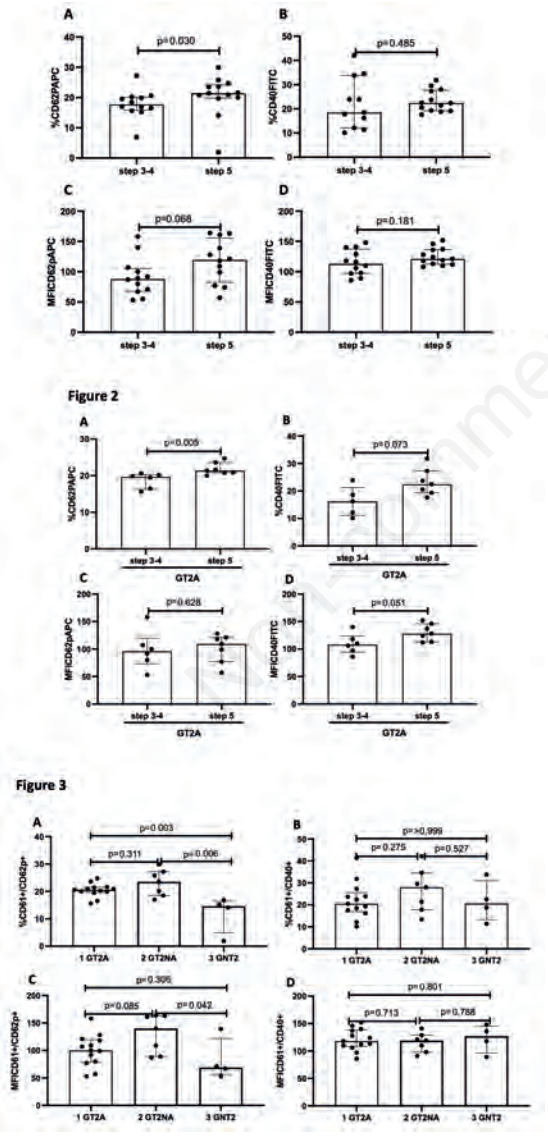

Figure 1.

PO120

A RARE CARDIOVASCULAR COMPLICATION OF COGAN'S SYNDROME

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Background: Cogan's syndrome (CS) is a rare inflammatory disease, which typically affects men and women between the second and fourth decade of life. It is characterized by interstitial keratitis, vestibuloauditory dysfunction and, rarely, systemic vasculitis. Cardiovascular complications include aortitis with aortic insufficiency, coronary artery involvement and stenotic vascular lesions.

Case Report: We report a rare case of 33-years-old woman, with a known medical history of CS, complicated by bilateral hearing loss and cochlear implants, left eye scleritis, previously treated with corticosteroids, methotrexate (MTX), and anti-TNFα monoclonal antibody infliximab (5 mg/kg every 6 weeks) due to relapsing-remitting course of the disease. Due to an acute salpingitis requiring salpingectomy, infliximab was suspended after two years of continuous treatment while MTX and low-dose of oral prednisone were maintained. Six months later, the patient presented to our emergency department (ED) with a worsening chest pain radiating to her left arm which onset within the previous 24 hours, associated with a syncopal episode. The patient complained of having exertional chest pain few times in a day in the last month. EKG showed signs of sinus rhythm with sustained diffuse ST-segment depression and ST-segment elevation in aVR and V1. Blood tests showed slightly elevated acute phase reactants (C-reactive protein and erythrocyte sedimentation rate were 12mg/dl and 53mm/h,respectively) and markedly elevated troponin levels (1052 pg/mL, n.v.<14 pg/ml). Aortic angiotomography showed irregular descending aortic contour with no signs of dissection and diffuse parietal thickening of the ascending aorta, suggestive of aortitis. Furthermore, ostial occlusion of the celiac trunk, superior mesenteric artery and right renal artery (as a consequence of aortic wall thickening) were described (Figure 1). A transthoracic echocardiographic showed an impaired left ventricular ejection fraction (LVEF=38%) with severe hypokinesia of the apex. The patient underwent an emergency coronary angiography that revealed the presence of a critical (99%) left main coronary artery ostial stenosis. After multidisciplinary discussion, a coronary angioplasty using a drug-eluting stent was chosen and successfully performed. Dual antiplatelet therapy with aspirin 100 mg/day and ticagrelor 90 mg twice/day was initiated, to be continued for 12 months. Considering the background diagnosis and the presence of diffuse aortitis complicated by coronary artery ostial narrowing, high dose of intravenous methylprednisolone (1g daily over 3

days with progressive tapering)was started, with absence of 18F-FDG accumulation on aortic wall at subsequent positron emission tomography (PET)scan. Currently, due to lack of randomised controlled trials there are no therapeutic recommendation for the treatment of CS-related vasculitis. Therefore, considering patient's medical history and based on previously reported cyclophosphamide use in ANCA-associated vasculitis, we started pharmacological treatment with cyclophosphamide at 15mg/kg, with sustained clinical and haemodynamic stability.

Conclusions: This case highlights the wide spectrum of CS manifestations and the importance of recognizing its potential for cardiovascular complications. Vestibulo-auditory and ocular involvement often manifest up to years apart and patients could develop aortitis many years after initial diagnosis. For these reasons, a continuous cardiovascular follow-up of every newly diagnosed case of CS should be performed to promptly diagnose and treat these life-threatening complications.

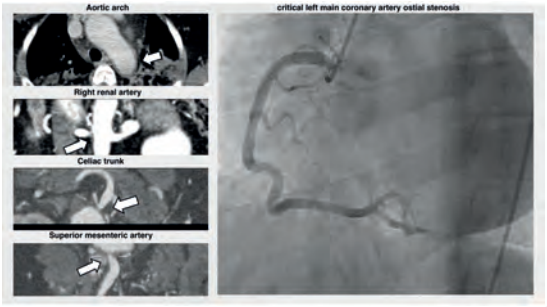

Figure 1.

P0121

THE COMPOUND PATHOGENIC EFFECTS OF A HOMOZYGOUS FRAMESHIFT VARIANT IN THE TRANSMEMBRANE REGION OF *GPIX*, CAUSING BERNARD-SOULIER SYNDROME, WITH A MISSENSE VARIANT IN *GPIB*

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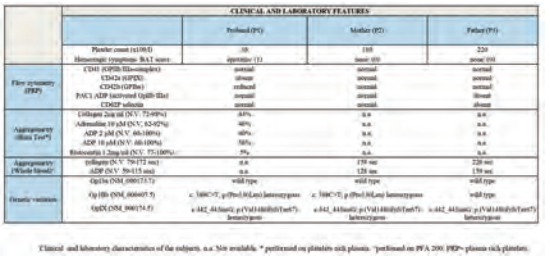
Background and Aims: The glycoprotein GPIb-IX-V complex is one of the major adhesion receptors expressed on the surface of circulating platelets and consists of GPIba, GPIbβ, GPIX and GPV. Deficiency or dysfunction of this complex cause a severe bleeding disorder known as the Bernard Soulier Syndrome (BSS). This work aims to describe an emblematic case of BSS, in which the attention is extended to the study of all the genes that form the complex, and to the mechanisms by which these genes interact.

Methods: The proband, 17-year-old, with severe thrombocytopenia, born from healthy non-consanguineous parents, was evaluated for adherent anti-platelet antibodies to exclude an immune thrombocytopenia, using flow cytometry. Based on platelet morphology, inherited thrombocytopenia was suspected, and immunophenotype characterization of platelet glycoproteins was performed by flow cytometry, followed by genetic testing on all exons and splice site regions of *GPIba*, *GPIbβ*, and *GPIX* genes by direct Sanger Sequencing. Platelet characterization and molecular genetic tests were performed for all three patients. Platelet aggregometry (Born) was performed on platelet rich plasma (PRP), using the agonists collagen, ADP, ristocetin, and adrenaline. Immunophenotype was conducted on PRP, incubated with monoclonal antibody against CD41, CD42a, CD42b CD49b, PAC1 ADP, CD62P ADP and analyzed using FC 500 Flow Cytometer.

Results: The proband presented stable low platelet counts and recurrent epistaxis. He manifested reduced aggregation to all stimuli with the Born method as reported in Table 1. Both parents were assessed for platelet aggregation test, and they presented longer aggregation times as reported in Table 1. Genetic investigation showed in the proband the homozygous variant p.Val148GlyfsTer67 in the coding region of the *GPIX* gene; this disrupts the normal protein sequence, looses 29 residues and produces a GPIX without the transmembrane domain. This has already been classified as pathogenetic. The proband inherited the variant from both heterozygous parents. In the proband and in the mother the heterozygous variant p.Pro130Leu was found in GPIbβ. This variant has never been described and was defined as variant of uncertain significance.

Table 1.



Conclusions: We found a simultaneous presence of two variants in GPIX and GPIbβ, never before described together in patients with BSS. p.Val148GlyfsTer67, identified in GPIX in the TM domain, produces a premature stop codon and deletes part of the TM domain and all N-terminal extracellular domain, important for formation and expression of GPIb-IX complex. This mutation is responsible for BSS and causes the loss of interaction between GPIX with GPIbβ. The second variant in the LRRNT domain of GPIbβ does not have a clear pathologic significance. It is possible that the second variant, p.Pro130Leu on GPIbβ, could have a worsening effect, altering the normal expression of GPIbα, destabilizing the whole complex GPIb-IX, as demonstrated by the platelet immunophenotype characterization, where the expression of GP1ba in the proband is reduced. In addition, the whole abolishment of GP complex expression found in immunophenotype could have caused the severe thrombocytopenia in the proband. This reduced expres-

sion of GPIX and GP1ba has not been found in the mother, because she manifested the two variant in heterozygosis, possibly permitting a sufficient expression of GP complex.

PO122

CYCLIC THROMBOCYTOPENIA IN MYELOPROLIFERATIVE NEOPLASM TREATMENT

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Background: Cyclic thrombocytopenia (CTP) is a rare disease, characterized by periodic platelet count oscillation. The pathogenesis is unknown, and CTP is associated with heterogeneous conditions. CTP may occur in patients with MPN during hydroxyurea (HU) treatment or spontaneously.
Case Report: We report on two patients who developed CTP during HU treatment and successive normalisation with Ruxolitinib. *Patient 1* (F, 60y): *post-ET MF* diagnosed in 2011, JAK2+, treated with ASA; in 2013 splenomegaly (18 cm) and CTP onset (Plt range 18-524, 28d cycle) were observed, with recurrent SVT (LMWH) and PE (AVK); in 2014 she started therapy with HU at low dose (3 t/w) due to thrombocytopenia, showing worsening of CTP oscillation (range 7-782), and once was transfused with one platelet pool (Plt 7, epistaxis). After 10 months she stopped HU therapy, and on March 2015 started Ruxolitinib, initially at 10 mg/d, then at 30 mg/d in two months, showing an initial increased fluctuation of platelets (range 123-1207) but with disappearance of thrombocytopenia; in ten weeks since Ruxolitinib at 30 mg/d no fluctuations of platelet count (range 251-372) nor CPT were observed anymore. *Patient 2* (M, 48y): *PV* (JAK2 V617F) was diagnosed in 2011, treated initially with ASA and phlebotomy, with a stable platelet count at baseline (range 597-658). On June 2012 started therapy with HU (7 t/w), showing CTP appearance (range 229-556, 28d cycle), and progressively increased fluctuations (range 94-996) as dosage was augmented to 14 t/w, without severe thrombocytopenia (nadir 94); in 2019 SVT (LMWH) then DVT (DOAC) occurred; in 2020 due to HU resistance, Ruxolitinib 20 mg/d was added, then increased to 40 mg/d in five months. Since 12 weeks from maximum dose, reduction of platelet fluctuation (range 259-392) and disappearance of CTP were observed (Figure 1).

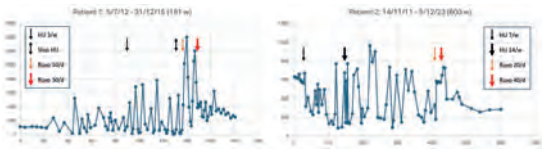

Figure 1.

Conclusions: In our two cases CTP was induced or amplified by HU treatment. Platelet fluctuation was reduced and then disappeared within 10-12 weeks after Ruxolitinib therapeutic dose. Disappearance of CTP was independent of HU interruption. Both patients evidenced a high JAK2 allelic burden (Pt1 98%, Pt2 89%), that might facilitate the CPT onset after starting HU therapy.[1] CPT may show very high platelet fluctuations, with possible thrombotic or haemorrhagic complications conditioning clinical outcomes in MPN patients.

Reference:
1. Zhang H, Villar-Prados A, Bussel JB, Zehnder JL. The highs and lows of cyclic thrombocytopenia. Br J Haematol. 2024 Jan;204(1):56-67.

PO123

LIGHT TRANSMISSION AGGREGOMETRY: PRELIMINARY RESULTS ON THE COMPARISON BETWEEN AUTOMATED SYSMEX CN-3000 AND MANUAL CHRONOLOG 490 AGGREGOMETERS

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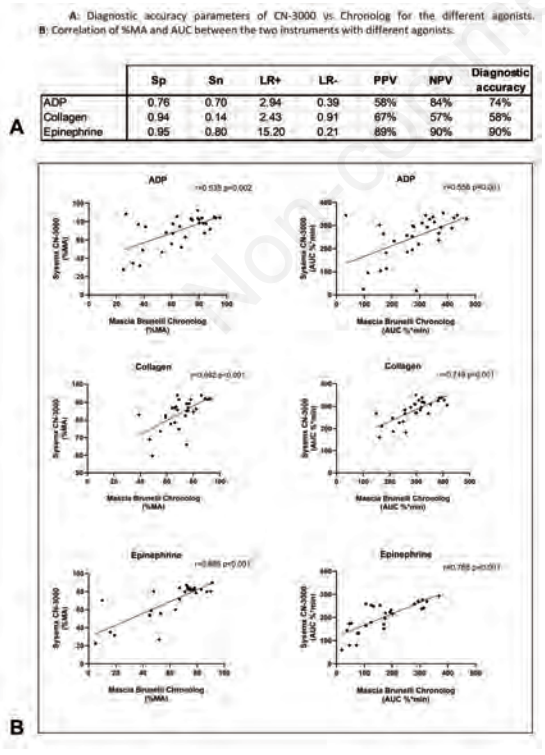
Background and Aim: Light transmission aggregometry (LTA) is the gold standard in platelet function diagnostic. LTA measures light transmission through a platelet-rich plasma (PRP) sample, which increases when platelets are induced to aggregate by different agonists. Manual aggregations require significant handling, are not standardized, and can usually be performed only in specialized laboratories. Studies on the previous generation of automated Sysmex CS-Series analyzers provided highly reliable platelet function tests with the potential to be standardized for use in clinical practice. However, no data are yet available on CN-3000 (Sysmex). This study aimed to compare the automated LTA system CN-3000 to the routine manual Chronolog 490 (Mascia Brunelli). We used two parameters: Maximum Aggregation in percentage (%MA) which is commonly used to evaluate platelet aggregation and Area Under the Curve (AUC) which is a parameter that embeds the time variable in addition to aggregation levels, better describing the aggregation dynamic.
Methods: Platelet aggregation study was performed on PRP obtained from 31 samples (17 patients with suspected platelet disorders and 14 healthy controls). ADP 2uM, epinephrine 5uM (CN-3000) or 10uM (Chronolog), and collagen 2ug/ml were used as agonists to induce platelet aggregation. The correlation between instruments of the%MA and AUC (%*min) after 10 (Chronolog) or 5 minutes (CN-3000) was evaluated using Spearman's rank correlation test. The ability of CN-3000 to discriminate between the target condition and health, in comparison to Chronolog, was evaluated using the 70% aggregation threshold supplied by the manufacturer. Diagnostic accuracy was assessed

calculating sensitivity (Sn), specificity (Sp), positive and negative predictive values (PPV and PPN), and positive and negative likelihood ratios (LR+ and LR-).
Results: CN-3000 requires a smaller sample volume of PRP per agonist (140uL) compared to the Chronolog (500uL), which is particularly helpful for the assessment of pediatric patients. In addition, PRP manipulation time is reduced and problems that can occur due to operator handling are overcome by the automatic simultaneous addition of agonists. Statistical analysis showed a good diagnostic accuracy for CN-3000 using Epinephrine (90%) and ADP (74%) while demonstrating less accuracy when using collagen (58%) (Figure 1A). The high level of correlation for both%MA and AUC between the two instruments (Figure 1B) further underline the reliability of CN-3000 and the possible usefulness of the AUC in describing platelet aggregation function.
Conclusions: Our data showed the potential utility of CN-3000 in platelet diagnostics. CN-3000 demonstrated to be comparable to Chronolog. Moreover, CN-3000 provides additional parameters that could better describe platelet function. Particularly, AUC, in addition to%MA, could be useful in the evaluation of aggregation curves since it better describes platelet aggregation kinetics. AUC is the most complete parameter as it is conditioned by both the maximum height of the curve and the slope and, therefore, can be considered as the best indicator of total platelet activity. Our next goal will be to implement the comparison between the two instruments, especially to establish the normal range references which are not defined yet.



	Sp	Sn	LR+	LR-	PPV	NPV	Diagnostic accuracy
ADP	0.76	0.70	2.94	0.39	58%	84%	74%
Collagen	0.94	0.14	2.43	0.91	67%	57%	58%
Epinephrine	0.95	0.80	15.20	0.21	89%	90%	90%

Figure 1.

PO124

USE OF DOAC AND INTRAVENOUS IMMUNOGLOBULIN IN A NEPHROPATHIC PATIENT WITH HEPARIN INDUCED THROMBOCYTOPENIA

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Heparin Induced Thrombocytopenia (HIT) is a prothrombotic immune-mediated drug-induced disease characterized by thrombocytopenia and arterial and/or venous thrombosis. The antithrombotic therapy in these patients is usually tricky, especially when comorbidities such as kidney disease requiring hemodialysis and atrial fibrillation worsen the clinical picture.We present the case of 80 years old man, admitted for acute upper limb arterial ischemia due to arterial embolism from a possible infective endocarditis involving aortic valve with surgical indication. Past medical history was significant for severe kidney disease needing hemodialysis (HD) and permanent atrial fibrillation (AF). During vascular surgery was used unfractioned heparin followed by anticoagulant therapy with LMWH. Over the course of the hospitalization there was a decrease of platelet count, up to 50% at 10th day. An ultrasound study of peripheral blood vessel, routinary in patient candidate to cardiac surgery, showed a dialysis catheter-related thrombosis. 4Ts score was 6/8. An immunoassay test for PF4/heparin antibodies resulted strongly positive (23,1/1 U). A confirmatory test was requested in order to asses the diagnosis, cytofluorimetry test resulted positive. The LMWH was immediately stopped, danaparoid was no available and the patient was considered unfitted for argatroban. The patient used special circuits for dialysis (at first anticoagulation with sulodexide was started, for clinical intolerance shifted to sodium citrate) and an off-label treatment with apixaban was started (2.5mg BID for the first 48 hours and subsequently 2.5mg OD) with close monitoring of hemoglobin, PT-INR, aPTT and antiXa concentration, was also performed a monitoring of trough level of apixaban. The platelet count was still of 10000-15000 after 10 days of therapy with apixaban; we decided to administrate intravenous immunoglobulins (IVIg), was started a short course therapy of 3 days, at the dose of 400mg/kg/die with a significant increasing in the platelet count (67000). VKA was introduced and the apixaban was stopped when the INR was >1,7.HIT in fragile patients with AF and in HD represent a really hard therapeutical challenge. Apixaban may be a valid alternative to other anticoagulants also in nephropathic patients.

PO125

PLATELET HYPERACTIVATION IN ELDERLY PATIENTS: ROLE OF CYCLOOXYGENASE 1

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Background and Aims: Aging is associated with an increase in platelet activity and a higher incidence of vascular and thrombotic diseases. Platelet hyperactivation is implicated in the established prothrombotic state, which explains the use of aspirin therapy, a suppressor of thromboxane synthesis by irreversible inhibition of cyclooxygenase-1 (COX-1), to prevent cardiovascular disease (CVD). Although ageing is associated with increased thrombotic risk, the mechanisms of platelet hyperactivation in ageing remain undescribed. We therefore investigated the role of cyclooxygenase-1 (COX-1) in elderly patients at high cardiovascular risk and hypothesised a mechanism of COX-1-mediated platelet hyperreactivity in ageing.
Methods: We conducted a prospective, single-centre cohort study involving 105 patients with atrial fibrillation (AF). The population was divided into age tertiles (mean age: 62 for tertile I, 75 for tertile II and 82 for tertile III). Serum COX-1 and serum thromboxane B2 (TxB2) concentrations were analysed by immunoenzymatic assay. In addition, subgroup analysis was performed on platelets isolated from AF patients divided into two age groups: <65 and >65 years. Platelet COX-1 expression by Western blot analysis and platelet activation by TxB2 levels were assessed in basal platelets and in platelets stimulated with arachidonic acid (AA) with or without scalar doses of ASA (25-50-100 μM).
Results: We observed that serum COX-1 levels were significantly different in the three groups of AF patients and increased with age ($p<0.001$). Similarly, TxB2 levels also increased with age ($p<0.001$). A direct correlation between TxB2 levels and COX1 levels was also observed in the univariate analysis. Furthermore, western blot analysis revealed higher COX1 expression in basal platelets from older patients (>65 years) than in younger patients (<65 years). In addition, in platelets isolated from elderly patients stimulated with AA, TxB2 inhibition was obtained with higher aspirin doses compared to younger patients as observed by a lower IC50 in younger than in older patients. Finally, the aspirin-induced reduction in TxB2 levels correlated negatively with COX1 expression.
Conclusions: In conclusion, these findings suggest that AF patients over 65 years of age have a significant increase in COX1 expression, which may contribute to age-related increased platelet hyperactivation and risk of CVEs.

PO126

NEUTROPHIL CATHEPSIN G AND PLATELET ACTIVATION IN TYPE 2 DIABETES: ROLE OF GLIFOZINS

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Background: Type 2 diabetes (T2D) is frequently complicated by cardiovascular disease (CVD). Platelet dysfunction plays a central role in the development of CVD in patients with T2D, as these patients have an increased thrombotic state associated with endothelial dysfunction and increased platelet reactivity. Neutrophils may contribute to platelet activation through the release of cathepsin G, a serine protease released upon neutrophil activation. There is also evidence that gliflozins reduce platelet activation, but their role in modulating neutrophil-derived cathepsin G release has never been studied in T2D.
Aim: In this study, we investigated whether serum cathepsin G is elevated in patients with type 2 diabetes mellitus (T2DM) and the relationship between cathepsin G levels and platelet activation.
Methods: In 32 patients with T2D on ongoing metformin therapy before and after Gliflozin therapy and in 20 healthy subjects (HS), Cathepsin G levels and platelet activation markers including soluble platelet selectin (sP-selectin), serum thromboxane B2 (TxB2) and soluble CD40 ligand (sCD40L) were analysed. The association between serum cathepsin and platelet activation was also investigated. We also performed an *in vitro* study to compare the effect of gliflozin on the release of cathepsin G and then on the interaction between platelets and neutrophils.
Results: Compared to HS, T2D patients had significantly higher blood levels of cathepsin G ($p<0.0001$). Furthermore, reduced circulating levels of cathepsin G and reduced markers of platelet activation were observed after gliflozin treatment. In addition, the reduction in serum cathepsin G levels significantly correlated with TxB2 ($rS=0.474$, $P=0.047$), sP-selectin ($rS=0.589$,

p<0.010) and sCD40L (rS=0.507, p<0.032) delta in T2D patients. Finally, an *in vitro* study on platelet-neutrophil mixture treated with gliflozin (10-30μM) resulted in higher cathepsin G levels in the medium than untreated platelet-neutrophil.
Conclusions: This study suggests that cathepsin G contributes to platelet activation in patients with T2D and that Gliflozins, in addition to their hypoglycemic effects, may have a beneficial effect on cathepsin G-mediated platelet-neutrophil interaction.

PO127

«PARATHYROID HORMONE INDUCES HUMAN NOX2-MEDIATED PLATELET ACTIVATION»

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Background and Aims: Parathyroid hormone (PTH) is the main endocrine regulator of extracellular calcium and phosphorus levels. Evidence suggests that PTH can act as an inflammatory mediator in several pathological settings including cardiovascular disease. To our knowledge, there are no current data on the possible effect of PTH on platelet activation and oxidative stress, but some investigators have reported some conflicting effects of PTH in platelets. Moreover, no studies have yet been performed to assess whether PTH may also be involved in the regulation of platelet activation and oxidative stress. Therefore, in the present study, we evaluated (i) platelet activation, oxidative stress, and endothelial dysfunction in patients with post-surgical chronic hypoparathyroidism (HypoPT), primary hyperparathyroidism (PHPT) and Healthy Subjects (HS); (ii) the effect of PTH on platelet activation and oxidative stress, as well as the putative intracellular pathway, and (iii) the expression of the PTH receptor (PTH1R) in human platelets.
Materials and Methods: This cross-sectional, single-center study took place at the bone outpatient clinic of the Metabolic Bone and Thyroid Disorders Unit of Fondazione Policlinico Universitario Campus Bio-Medico of Rome between March 2021 and July 2023. Patients with HypoPT (n=40), defined as hypocalcemia in the presence of a low or inappropriately normal PTH level, patients with PHPT (n=40) defined as elevated or unsuppressed PTH concentrations, and HS (n=40) were consecutively enrolled. In these subjects, we evaluated platelet activation, oxidative stress, and endothelial dysfunction. Moreover, *in vitro*, platelets from HypoPT patients and HS were incubated with increasing doses of PTH (13, 49 and 85 pg/mL) and platelet aggregation, biomarkers of oxidative stress (NOX2 activation and H2O2 production) and thrombus formation were analyzed. Finally, we evaluated by western blot analysis the expression of PTH1R in platelets from HypoPT patients and HS.
Results: The results showed increased levels of platelet activation (evaluated by platelet aggregation, sP-selectin, sCD40L and TxB2), oxidative stress (evaluated by H2O2, NOX2 activation and HBA) and endothelial dysfunction (evaluated by sICAM-1, SVCAM-1 and NO bioavailability) in PHPT patients compared to HypoPT and HS and in HypoPT compared to HS. The *in vitro* study demonstrated that PTH incubated with platelets from HypoPT patients enhanced platelet aggregation, sP-selectin levels, and oxidative stress by increasing NOX2 activation and H2O2 production, compared to PTH-treated platelets from HS. Finally, PTH was able to increase thrombus formation in HypoPT patients compared to HS. No difference was observed in PTH1R expression in platelets from HypoPT patients and HS.
Conclusions: These results provide new insight into the mechanisms of PTH-induced platelet activation via NOX2-related oxidative stress. Our findings may lead to the development of new pharmacological strategies for patients suffering from chronic hypoparathyroidism who take PTH as replacement drug therapy or to estimate the possible cardiovascular risk of these subjects.

PO128

ANALYSIS OF PATIENTS WITH INHERITED PLATELET DISORDERS: A MONOCENTRIC REAL-LIFE STUDY

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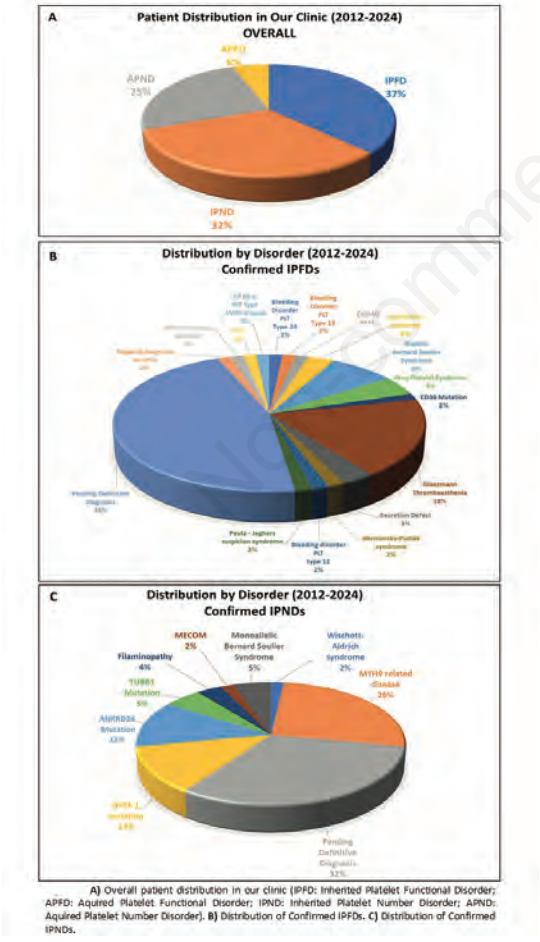
Background and Aim: Inherited platelet disorders (IPDs) are rare and heterogeneous diseases that include inherited platelet number disorders (IPNDs) and inherited platelet function disorders (IPFDs). These disorders have a wide clinical spectrum ranging from no bleeding symptoms to life-threatening bleeding diathesis and to predisposition to severe non hemostatic diseases involving other organs during life. IPNDs are often undiagnosed or misdiagnosed as immune thrombocytopenias. IPFDs are underdiagnosed because platelet function tests are not widely used or available. For these reasons, the management of IPDs can be difficult and the patient

quality of life can be poor. Recent advances in the knowledge of a growing number of IPDs together with the increased use of genetic testing required revision of many undiagnosed patients with suspected IPDs. The focus of this study is to describe the clinical, laboratory and genetic characteristics of patients investigated in our clinic for suspected or identified IPDs.

Methods: We retroactively collected data from 177 patients evaluated for a suspected platelet disease in the Unit of Bleeding and Thrombotic Diseases of Fondazione Policlinico A. Gemelli IRCCS from 2012 to April 2024. Data retrieved were the following: clinical history, ISTH-BAT score, platelet count, mean platelet volume (MPV), bleeding time, light transmission aggregometry, cytofluorometric assessment of major platelet glycoproteins and of platelet secretion, genetic analyses. Confirmed IPFDs and IPNDs were considered those cases with a platelet disorder that could not be considered acquired, based on clinical and laboratory results.

Results: Among 177 patients investigated for a platelet disorder, 65 received a diagnosis of IPFDs, 57 a diagnosis of IPNDs, 55 a diagnosis of an acquired platelet function or platelet number disorder. (Figure 1A). In Figure 1 B-C, distributions of confirmed IPFDs and IPNDs are reported.



A) Overall patient distribution in our clinic (IPFD: Inherited Platelet Functional Disorder; APFD: Aquired Platelet Functional Disorder; IPND: Inherited Platelet Number Disorder; APND: Aquired Platelet Number Disorder). B) Distribution of Confirmed IPFDs. C) Distribution of Confirmed IPNDs.

Figure 1.

Conclusions: This study suggests that the prevalence of IPDs may be higher than expected. The clinical picture of IPDs might not be limited to bleeding symptoms and has become more variegated and complex, with frequent association with other congenital manifestations or predisposition to other severe diseases occurring during life. Hemostasis and thrombosis specialists should become familiar with these rare diseases to offer patients appropriate referral for the diagnosis, to optimize their management and to improve their quality of life.

PO129

MORE ON RETICULATED PLATELET PRO-COAGULANT ROLE IN PATIENTS WITH CIRRHOSIS

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Background and Aim: In liver cirrhosis the increased platelet turnover implies the release of "emergency platelets", also called reticulated platelets (RePLTs), which would contrast bleeding events that can occur due to reduced synthesis of hepatic-dependent coagulation factors and decreased platelet count. Reticulated platelets are bigger and more reactive than mature platelets; they have a high content of ribonucleic acid (RNA) and are directly released by megakaryocytes to contrast peripheral platelet destruction, which is one of the major mechanisms responsible for thrombocytopenia in cirrhosis. However, the role of RePLTs in the hemostatic balance in cirrhosis is completely unknown. The aim of this study is to compare the surface antigenic properties of RePLTs *versus* mature platelets in cirrhotic patients by using new generation flow cytometry.

Methods: Platelet rich plasma (PRP) from consecutive patients with liver cirrhosis of different severity (n=25) and healthy subjects (n=14) was collected for analysis by CytoFLEX-SRT cytometer (Beckman Coulter). Size gate was obtained by using a mix 1:1 of fluorescent polystyrene beads of known size including Megamix and Flow-Count for sizes 0.9, 3 and 10 µm respectively. Anti-CD41 (P-selectin) and SYTO-13 (RNA) positivity defines RePLTs in the morphological gate set between the 3 µm and 10 µm beads population diameter. Based on SYTO-13 fluorescence positivity, three populations were defined: the first quintile of SYTO-13-low platelets, that is the 20% of platelet population with SYTO-13 negative fluorescence (mature platelets); the fifth quintile of SYTO-13-high platelets (RePLTS) and the 1% of the most SYTO-13 positive RePLT population obtained with a line starting at the origin and encompassing 1-1,5%, which is a subpopulation of SYTO-13-high platelets. Additionally, the expression of Annexin V (phos-

phatidylserine) and anti-CD62P (P-selectin) were used to evaluate RePLTs and mature platelet activation state.
Results: The percentage of RePLTs in cirrhotic patients is slightly higher than in healthy controls (mean [standard deviation]: 1,02% [0,71%] *vs.* 0,82% [0,32%] respectively p=0.5). In cirrhosis, the proportion of SYTO-13-high platelets (RePLTs) triple positive for $CD41^+$Annexin V^+CD62P^+ was higher than SYTO-13-low platelets (mature platelets) (19% [27,4%] *vs.* 10,4% [26,5%] respectively p<0.0001). In addition, we observed that the subpopulation 1% of the most SYTO-13 positive RePLTs showed a greater expression of $CD41^+$Annexin V^+CD62P^+ compared to SYTO-high platelets (47% [32%] *vs.* 19% [27,4%] respectively p<0,0001) (Figure 1A), suggesting that RePLTs with the highest amount of RNA are the most activated. Furthermore, the subpopulation 1% RePLTs $CD41^+$Annexin V^+CD62P^+ was higher in cirrhosis than in healthy subjects (47% [32%] *vs.* 25,9% [18,5%] respectively p=0.015) (Figure 1B-D).
Conclusions: The number of RePLTs is higher in cirrhosis than in healthy controls. In both cirrhotic patients and healthy subjects, RePLTs expressed more activation markers than mature platelets and RePLTs with the highest amount of RNA are the most activated. Furthermore, RePLTs in cirrhosis are more activated than RePLTs in healthy controls, suggesting a hyperactive state. Finally, a better understanding of RePLTs properties may improve the knowledge of cirrhotic coagulopathy, leading to a better identification of patients at higher risk of thrombosis and disease progression.

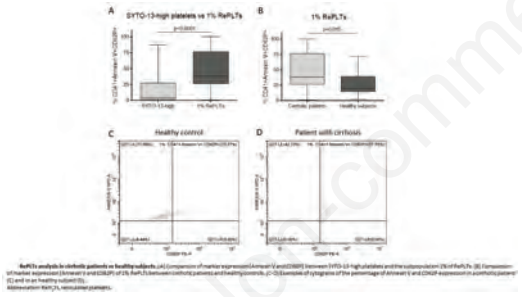

Figure 1.

PO130

OPTIMIZING THE EXPERIMENTAL CONDITIONS FOR ASSESSING -GALACTOSE EXPOSURE IN HEALTHY CONTROLS AND THROMBOCYTOPENIC PATIENTS

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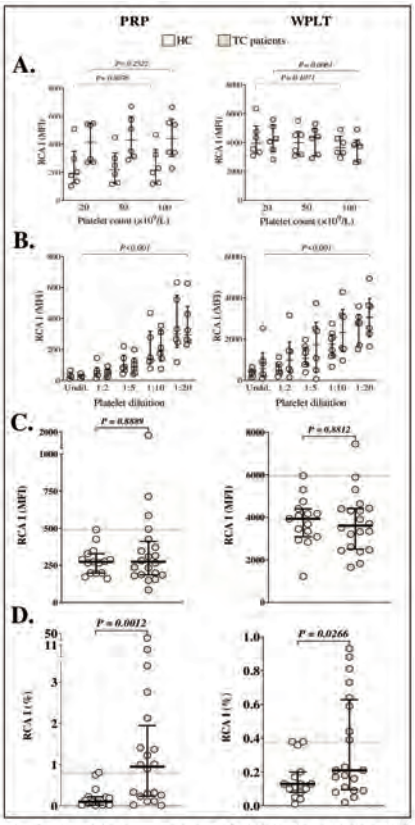
Background and Aims: Platelet desialylation leads to β-Galactose exposure on the platelet surface, which accelerates platelet clearance and potentially induces thrombocytopenia. An accurate assessment of β-galactose exposure by Flow Cytometry (FC) is crucial for understanding its pathophysiological significance, as several variables may affect the results. The aim of this study is to determine the optimal conditions for assessing β-galactose exposure on the platelet surface by FC in Healthy Controls (HC) and in thrombocytopenic (TC) patients, who typically exhibit higher levels of desialylated platelets.
Methods: We evaluated β-Galactose exposure by FC using Ricinus Communis Agglutinin I (RCA I) in 15 HC (median platelet count $240x10^9$/L, IQR: 199-256) and 20 TC patients (median platelet count $58x10^9$/L, IQR: 33-88) in both Platelet-Rich Plasma (PRP) and Washed Platelet (WPLT) samples. We evaluated the impact of different platelet counts (20, 50, and $100x10^9$/L) diluted in Platelet Poor Plasma (PPP) or Tyrode's solution for PRP and WPLT, respectively. Platelet dilutions (1:2, 1:5, 1:10, 1:20) were prepared by dilution in phosphate-buffered saline (PBS) or Tyrode's solution and incubated with RCA I at specified concentrations at room temperature for 30 minutes. The reaction was stopped with PBS and 10.000 events within the platelet gate were acquired by FC. β -galactose exposure was expressed as median fluorescence intensity (MFI) of RCA I and as percentage of RCA I-positive platelets.
Results: Platelet count did not affect RCA I-MFI in PRP samples, whereas a trend towards a decrease in RCA I-MFI was observed in WPLT samples at platelet count of $100x10^9$/L, particularly in TC patients (Figure 1, Panel A). The dilution of samples positively influenced RCA I-MFI, with the maximum fluorescence intensity occurring at 1:20 dilution (Figure 1, Panel B). Comparisons between TC patients and HC showed no statistically significant differences in RCA I-MFI across both PRP and WPLT samples (Figure 1, Panel C), even after adjusting for platelet size (forward scatter), to account for the larger platelets typically seen in TC patients. Notably, RCA I-MFI values exceeding the 95th percentile of HC were seen in 20% of PRP and only in 5% of WPLT samples among TC patients. Furthermore, samples of TC patients displayed a significantly higher percentage of RCA I-positive platelets compared to HC (Figure 1, Panel D), with 55% of PRP and 40% of WPLT samples from TC patients showing RCA I-positive platelets above the 95th percentile of HC.
Conclusions: Our study establishes optimal conditions for evaluating β-galactose on platelets, employing a refined FC protocol that is effective across different subject groups (TC patients and HC) and at various platelet counts. Our results emphasize the utility of PRP samples over WPLT samples for detecting subtle variations in β-galactose exposure. Notably, the percentage of RCA I-positive platelets was a more discriminative parameter than RCA-I-MFI for evaluating the extent of desialylation across different sample types. In fact, while TC patients and HC have a similar number of desialylated sites per platelet (expressed as RCA I-MFI), the prevalence of desialylated platelets is greater in TC patients, highlighting a significant pathological distinction that may contribute to the increased platelet turnover

observed in these patients. In conclusion, our improved methods provide a strong basis for further studies on platelet disorders.



Panel A: The effect of platelet count variation on RCA I-MFI in platelet rich plasma (PRP) and washed platelet samples (WPLT) from 6 healthy controls (HC) and 6 thrombocytopenic (TC) patients. Panel B: The effect of dilution factors on RCA I-MFI in platelet rich plasma (PRP) and washed platelet samples (WPLT) from 6 healthy controls (HC) and 6 thrombocytopenic (TC) patients. Panel C: β-galactose exposure expressed as RCA I-MFI in platelet rich plasma (PRP) and washed platelet samples (WPLT) from 15 healthy controls (HC) and 20 thrombocytopenic (TC) patients. Panel D: β-galactose exposure expressed as percentage of RCA I-positive platelets in platelet rich plasma (PRP) and washed platelet samples (WPLT) from 15 healthy controls (HC) and 20 thrombocytopenic (TC) patients.
Data are expressed as medians with interquartile ranges (25th-75th). The 95th centile for β-galactose exposure was determined in HC and used as the threshold. Statistical significance was assumed for p-values <0.05.

Figure 1.

PO131

INHERITED PLATELETS DISEASE AND ACQUIRED THROMBOCYTOPENIA MAY COEXIST: THE INTRIGUING HISTORY OF A LITTLE CHILD

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Background: Inherited platelet disorders, including platelet storage pool diseases (SPDs), manifest in various bleeding symptoms, with severity often categorized based on their effects on either the surface receptors or internal structures of platelets. This rare condition, characterized by defects in platelet granules, exhibits broad phenotypic variability, ranging from mild bruising to severe hemorrhages. Diagnosis involves specialized analyses such as platelet aggregation and genetic studies, necessitating a multidisciplinary approach for management.
Case Report: Our case report describes a child with recurrent epistaxis, initially diagnosed with immune thrombocytopenia. Subsequent presentations led to suspicion of von Willebrand disease, but further examinations revealed a platelet function disorder. Genetic testing confirmed mutations associated with SPD. Treatment options include desmopressin, antifibrinolytic agents, and platelet transfusions, tailored to individual needs. The discussion underscores the diverse manifestations of SPD, emphasizing the importance of thorough diagnostic assessments.
Conclusions: Treatment strategies aim to alleviate bleeding symptoms and mitigate associated risks, with a strong focus on personalized care. Challenges in managing SPD include missed diagnoses and the influence of genetic variations on disease severity. Ultimately, early detection and individualized therapies are essential for effectively managing SPD, underscoring the ongoing need for research to enhance outcomes for affected individuals.

PO132

ROLE OF MYELOID-RELATED PROTEIN (MRP)-8/14 IN SUBOPTIMAL RESPONSE TO ASPIRIN IN PATIENTS AT HIGH CARDIOVASCULAR RISK: BETWEEN SYSTEMIC INFLAMMATION AND THROMBOTIC COMPLICATIONS

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Background and Aims: MRP-8/14, an inflammatory protein, expressed in leukocytes and in part derived from platelets, represents a marker of residual thromboxane-dependent platelet activation. In patients with acute coronary syndromes in treatment with low-dose aspirin (ASA) the levels of circulating MRP-8/14 were correlated with TX-dependent platelet activation. The variable turnover of aspirin's target, platelet COX-1, is the most compelling determinant of interindividual variability in aspirin response. Recently, MRP-8/14-GPIbα axis has been identified as a novel prothrombotic pathway that triggers the formation of procoagulant platelets accelerating fibrin generation and thrombosis, highlighting the importance of thromboinflammation in atherothrombo-

sis. Our aim was to identify the relationship between MRP-8/14 and suboptimal aspirin (ASA) response in patients at high cardiovascular risk.

Methods: We evaluated the changes in MRP4, a protein known to extrude ASA, MRP-8/14 and miR-21 expression in high CV risk patients (100 with and without type 2 diabetes mellitus (T2DM)) in chronic treatment with ASA (100 mg/day), for cardiovascular prevention. Blood sampling was performed at 10 (T10) and 24 hours (T24) after a witnessed administration of ASA. Patients were stratified into tertiles based on the slope of serum TXB2. The first and third tertiles were compared.

Results: Third tertile patients, with accelerated recovery of COX-1, tended to be more obese (p=0.053) and with a higher BMI (=0.011), waist circumference (p=0.002), WHR (p=0.010) and white blood cells count (p= 0.050) than the patients of first tertile. We observed higher levels of MRP-8/14, in patient's 3rd *vs* 1st tertile (p=0.010) and inversely (rho=-0.182, p=0.043) and directly correlated (rho= 0.279, 0=0.010) with platelet and circulating miR21 levels, respectively. Platelet protein MRP4 was also increased in third tertile patients (p<0.001) with inverse (rho=-0.665, p<0.001) and direct (rho=0.471, p=0.003) correlation with platelet and circulating miR21 respectively. MRP8/14 was directly correlated with MRP4 (rho=0.410, p=0.038). After one hour of treatment with increasing doses of recombinant MRP8/14 (rMRP-8/14), we observed a dose-dependent upregulation of MRP4 in DAMI cells (UNTR *vs* 0.5, p=0.047; UNTR *vs* 1, p=0.008). Stimulation of DAMI cells with rMRP8/14 induced an early decrease in platelet miR-21 after 1-hour (p=0.002) and a subsequent increase of the miR-21 in the supernatant. To corroborate the relationship with accelerated recovery of COX-1, both miR-21 (platelet: rho=-0.216 p=0.020, circulating: rho=0.191, p=0.066) and MRP4 (rho=0.369 p=0.064), were correlated with sTXB2 slope.

Conclusions: Inhibition of platelet COX-1 activity by standard once-daily aspirin may be incomplete due to elevated MRP4 levels, responsible for aspirin extrusion. In patients who have accelerated recovery of COX-1, higher levels of MRP-8/14 are associated with upregulated MRP4 which in turn may be responsible for extrusion of both aspirin and miR-21. Higher thromboinflammatory state, as reflected by upregulation of MRP-8/14, may modulate extrusion of aspirin and possibly platelet miR-21 levels. Circulating MRP-8/14 may be a potential biomarker to predict response to ASA treatment in high-risk cardiovascular patients.

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