

Cancer complicated by thrombosis and thrombocytopenia: still a therapeutic dilemma

Yishi Tan,^{1,2} Marc Carrier,³ Nicola Curry,^{4,5} Michael Desborough,^{4,5} Kathryn Musgrave,⁶ Marie Scully,^{1,2} Tzu-Fei Wang,^{3*} Mari Thomas,^{1,2*} Simon J. Stanworth^{4,5,7*}

¹Department of Haematology, University College London Hospital, United Kingdom; ²Institute of Cardiovascular Science, University College London, United Kingdom; ³Division of Hematology, Department of Medicine, University of Ottawa, Ottawa Hospital, ON, Canada; ⁴Department of Haematology, Oxford University Hospitals NHS Foundation Trust, United Kingdom; ⁵Radcliffe Department of Medicine, University of Oxford, United Kingdom; ⁶Department of Haematology, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, United Kingdom; ⁷NHSBT, Oxford, United Kingdom

*Joint senior authors.

ABSTRACT

Individuals who have thrombocytopenia and cancer-associated thrombosis (CAT) are difficult to manage because they have a high risk of bleeding and recurrent thrombosis. The International Society on Thrombosis and Haemostasis guidelines for the management of thrombocytopenia in patients with CAT suggest two main approaches: either complete anticoagulation with transfusion support if

necessary, or dose-modified anticoagulation while the platelet count is $<50 \times 10^9/L$. Nevertheless, rather than being based on information from randomized controlled trials (RCTs), these recommendations were based on expert consensus. Recent research from two different countries has shown how this cohort's management and results vary widely. While the United Kingdom study, Cancer-Associated Venous Thrombosis and Thrombocytopenia, found no significant differences in bleeding or recurrent thrombosis between full dose and modified dose groups, the North American Thrombocytopenia Related Outcomes with Venous thromboembolism study demonstrated a significantly lower risk of bleeding events in those receiving modified dose anticoagulation compared to full dose, without an increased risk of recurrent VTE. Therefore, an RCT is required to assess the best course of action for patients with CAT and thrombocytopenia. To define the standard of care for the management of patients with CAT and thrombocytopenia, a full-scale trial called the START randomized trial (STrategies for Anticoagulation in patients with thRombocytopenia and cancer-associated Thrombosis) is an international, multi-site pilot study that compares the use of platelet transfusions plus higher dose anticoagulation to modified dose anticoagulation in patients with thrombocytopenia and CAT receiving anticoagulation.

Correspondence: Simon J. Stanworth, NHS Blood and Transplant, Level 2, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9BQ, United Kingdom.
E-mail: simon.stanworth@nhsbt.nhs.uk

Conference presentation: paper presented at the 12th International Conference on Thrombosis and Hemostasis Issues in Cancer (17-19 May 2024, Bergamo, Italy).

Key words: cancer-associated thrombosis; thrombocytopenia.

Acknowledgments: we thank the support of colleagues in discussions on this research topic, including A Falanga, A Leader, D Prati, M Marchetti, and H Tencate.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare the existence of a potential conflict of interest.

Funding: none.

Ethical approval and consent to participate: not applicable.

Availability of data and material: the data for TROVE and CAVEaT studies have been published.

Received: 15 January 2024.

Accepted: 5 April 2024.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2024

Licensee PAGEPress, Italy

Bleeding, Thrombosis and Vascular Biology 2024; 3(s1):115

doi:10.4081/btvb.2024.115

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

Introduction

Healthcare professionals are commonly faced with the dilemma of managing patients with cancer complicated by both thrombocytopenia and thrombosis. Treatment decisions need to balance the risks of bleeding and the extension of thrombosis. Thrombocytopenia is common in patients with cancer and may be multifactorial, with contributing systemic chemotherapy, malignant bone marrow infiltration, or infection.¹ Whilst thrombocytopenia may increase the risk of bleeding, it confers no protection against thrombosis recurrence in patients with cancer-associated thrombosis (CAT).^{2,3} This adds an extra layer of complexity to an already difficult balance between the competing risks of bleeding and thrombotic complications.

How common is cancer-associated thrombosis in thrombocytopenic patients with solid and hematological malignancies?

The estimated lifetime risk of developing cancer in the United Kingdom (UK) is 50% and cancer is a significant risk factor for venous thromboembolism (VTE).⁴ The risk of VTE is 7-11-fold higher in patients with cancer compared to those without cancer,⁵ with the risk rising to 23-fold if receiving chemotherapy or immunotherapy.⁶ The incidence of CAT is increasing, likely due to thrombotic risks observed with some newer therapeutic agents, patients living longer with cancer due to advancement in therapies,⁶ as well as increased vigilance of CAT over the last 20 years.⁵

CAT is the second leading cause of mortality in patients with cancer.⁷ Thrombocytopenia (platelet count $100 \times 10^9/L$ or less) is present in approximately 1 in 2 patients with CAT and hematological malignancies and 1 in 5 patients with CAT and solid tumors.⁸

Amongst patients with hematological malignancies, cohorts that are particularly at risk of thrombosis include patients with: myeloma and on immunomodulatory drugs;⁹ acute lymphoblastic leukemia receiving L-asparaginase; acute promyelocytic leukemia, who are prone to thrombotic as well as bleeding complications due to disseminated intravascular coagulopathy,^{10,11} and patients who have undergone hematopoietic stem cell transplant.¹²

Risk factors for thrombosis in ambulatory patients with solid organ tumors receiving chemotherapy include cancer type and treatment-related factors. Although risk prediction scores have been validated to predict patients at higher risk of CAT,¹³ most patients who developed CAT were not identified as high risk by current risk assessment models.¹⁴ It should also be noted that the majority of patients included in the development of the risk scores had solid tumors rather than hematological malignancies.¹¹

What are the consequences of cancer-associated thrombosis in thrombocytopenic patients with cancer?

A recent systematic review and meta-analysis found high risks of both recurrent VTE (2-4%/100 patient months) and bleeding (major bleeding: 2-4%/100 patient months, total bleeding: 3-13%/100 patient months) in patients with CAT and thrombocytopenia (platelet count $<100 \times 10^9/L$), regardless of the anticoagulation management strategies.¹⁵ This adds to the findings of a previous systematic review in 2018, which found that 27% of patients with CAT experienced recurrent VTE regardless of their management, whilst 13% of anticoagulated patients developed major bleeding.³ In addition, CAT has a significant impact, including increased morbidity, reduced quality of life, interruptions in cancer treatment, significant healthcare system costs, as well as a 3-fold reduction in one-year survival rate compared to cancer patients without VTE.^{6,16,17}

Overview of current management of cancer-associated thrombosis in thrombocytopenic patients

The optimal management options need to consider the competing risks of bleeding and thrombosis extension. Therefore, one common practice has seen a dual approach of raising platelet count by platelet transfusion and treating with anticoagulants,¹⁸ based on the unproven assumption that anticoagulation would be safer above a certain platelet threshold. However, here is where the uncertainties start, with no randomized controlled trials (RCTs) guiding the target platelet count, dose of platelet transfusion, or frequency of monitoring and dose of anticoagulation.

Both platelet transfusions and anticoagulants have inherent risks. Platelet transfusions have risks common to all biological agents and blood components and have been implicated in bacterial and viral transfusion-transmitted infections, transfusion-related acute lung injury, allergic reactions, and febrile non-hemolytic transfusion reactions.¹⁹ These risks of platelet transfusion have been reinforced by findings of recent randomized trials comparing more liberal and restrictive policies for platelet transfusion. For example, several RCTs have reported evidence of additional harm in patient cohorts needing platelet transfusions, including neonates with thrombocytopenia and patients presenting with acute hemorrhagic strokes associated with antiplatelet medications.^{20,21} It is likely that these risks reflect the immunological effects of platelets, which have *in vivo* actions beyond hemostasis.

What do guidelines say about management?

There is a lack of consensus on the management of CAT in patients with thrombocytopenia, with current international guidance informed by observational studies and expert opinions rather than evidence from RCTs.^{18,22} The 2018 guidance from the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee recommends a risk-stratified management approach according to the acuity of the thrombus, the risk of thrombosis progression, and platelet count (Table 1).

What is the current practice?

Despite the international guidelines, audits and studies demonstrate inconsistent and variable practice, likely reflecting the lack of strong evidence behind the guideline recommendations. Two international studies have recently demonstrated the heterogeneity in the management of this cohort, the key findings of which are summarized in Table 2.^{23,24} The Cancer-Associated Venous Thrombosis and Thrombocytopenia (CAVEaT) UK study in patients with hematological malignancies showed that 47% of patients with higher risk thrombosis and 5% with lower risk thrombosis were managed according to the ISTH guidance. There was variation in the use of platelet transfusions. Changes in anticoagulation were observed in 51% of patients by 90 days. Mortality was 15% at 28 days and significant morbidity was

demonstrated.²⁴ The North American Thrombocytopenia Related Outcomes with Venous thromboembolism (TROVE) study also found that changes in anticoagulation choice were frequent, with less frequent alterations in anticoagulation intensity.²³

Interestingly, the two studies revealed different findings. The

TROVE study showed a significantly reduced risk of bleeding events in those receiving modified dose anticoagulation compared to full dose, without an increased risk of recurrent VTE. In contrast, the CAVEaT study showed no significant differences in bleeding or recurrent thrombosis between full-dose and mod-

Table 1. Summary of the 2018 International Society on Thrombosis and Haemostasis Scientific and Standardization Committee guidance on the management of cancer-associated thrombosis in patients with thrombocytopenia.

Risk category	Baseline platelet count at the time of index VTE	Management
Any	>50×10 ⁹ /L	Therapeutic dose anticoagulation without platelet transfusion support
Higher risk* acute [#] CAT	<50×10 ⁹ /L	Platelet transfusion support, target >40-50×10 ⁹ /L, and therapeutic anticoagulation (LMWH/UFH)
Lower risk ^{&} acute CAT, subacute or chronic [^] CAT	25-50×10 ⁹ /L	Reduced dose (50% of therapeutic dose) LMWH, or Prophylactic dose LMWH
	<25×10 ⁹ /L	Withhold anticoagulation while platelet <25×10 ⁹ /L

*Higher risk CAT, including but not limited to: symptomatic segmental or more proximal pulmonary embolism (PE), proximal deep vein thrombosis, history of or recurrent/progressive thrombosis; [#]Acute CAT, within the first 30 days of index venous thromboembolism; [&]Lower risk CAT, including but not limited to: distal deep vein thrombosis, incidental subsegmental pulmonary embolism, catheter related thrombosis; [^]Subacute or chronic CAT, >30 days since index venous thromboembolism. VTE, venous thromboembolism; CAT, cancer-associated thrombosis; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

Table 2. A comparison between Thrombocytopenia-Related Outcomes with Venous thromboembolism and Cancer-Associated Venous Thrombosis and Thrombocytopenia studies.^{23,24}

	TROVE	CAVEaT
Region	North America	United Kingdom
Design	Prospective, observational, multicentre cohort study	Prospective, observational, multicentre cohort study
Number of patients	121	105
Type of malignancy		
• Hematological	85/121 (70%)	105/105 (100%)
• Solid tumor	36/121 (30%)	0%
Index VTE event:		
• Upper limb DVT	48/121 (40%)	44/105 (42%)
• Lower limb DVT	49/121 (40.5%)	16/105 (15%)
• PE	45/121 (37%)	35/105 (33%)
• Other	4/121 (3%)	10/105 (9.5%)
Baseline platelet threshold for enrolment	<100×10 ⁹ /L	<50×10 ⁹ /L
Initial anticoagulation	<ul style="list-style-type: none"> • Full dose LMWH, UFH or DOAC: 75/121 (62%) • Modified dose LMWH, UFH or DOAC: 33/121 (27%) • No anticoagulation: 13/121 (11%) 	<ul style="list-style-type: none"> • Full dose LMWH or UFH: 56/105 (53%) • Modified dose LMWH: 33/105 (31%) • DOACs: 4/105 (4%) • No anticoagulation: 12/105 (11%)
Thrombosis recurrence according to initial anticoagulation	At 60 days: <ul style="list-style-type: none"> • Full dose anticoagulation: 5.6% (95% CI 0.2-11) • Modified dose anticoagulation: 0% 	At 28 days: <ul style="list-style-type: none"> • Full dose LMWH or UFH: 4% • Modified dose LMWH: 4% • DOACs: 0% • No anticoagulation: 0%
Major bleeding according to initial anticoagulation	At 60 days: <ul style="list-style-type: none"> • Full dose anticoagulation: 12.8% (95% CI 4.9-20.8) • Modified dose anticoagulation: 6.6% (95% CI 2.4-15.7) • Fine Gray hazard ratio 2.18 (95% CI, 1.21-3.93) 	At 28 days: <ul style="list-style-type: none"> • Full dose LMWH or UFH: 3% • Modified dose LMWH: 4% • DOACs: 0% • No anticoagulation: 0%
Conclusions as reported by authors	Modified dose anticoagulation may be a safe alternative to treatment dose anticoagulation	No clear relationship between platelet transfusion threshold, anticoagulation dose reduction threshold and risk of thrombosis progression or major bleeding

TROVE, Thrombocytopenia Related Outcomes with Venous thromboembolism; CAVEaT, Cancer-Associated Venous Thrombosis and Thrombocytopenia; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin; UFH, unfractionated heparin; DOAC, direct oral anti-coagulants; CI, confidence interval.

ified-dose groups. The reasons for these differences were not clear but might reflect aspects of the study methodology including inclusion criteria and differences in baseline characteristics (Table 2). While these studies advanced the field by providing prospective data for the first time for patients with CAT and thrombocytopenia, the observational nature and non-randomized design of the studies were potential confounders and limited the strength of any conclusions. The results are hypothesis-generating and not yet practice-changing.

What current research is happening?

There is a pressing need for a more robust design of the study to evaluate the optimal management strategies (including anticoagulation and platelet transfusion) in patients with CAT and thrombocytopenia. Patient groups are integral to designing studies and disseminating findings. Patients with hematological cancers frequently emphasize the importance of quality of life and functional recovery in addition to outcomes such as survival, and complications such as thrombosis are viewed as a barrier to rehabilitation.

An example of a currently recruiting study is the START randomized trial (S**T**rat^egies for Anticoagulation in patients with th**R**ombocytopenia and cancer-associated Th**R**ombosis) (NCT05255003) (Figure 1). This is an international, multi-site pilot trial assessing the use of platelet transfusions plus higher dose anticoagulation compared to modified dose anticoagulation in patients with thrombocytopenia and CAT receiving anticoagulation, with planned participating sites in Canada and the UK. The study has been reviewed and supported by patient represen-

tatives at the Canadian Venous Thromboembolism Research Network, and Thrombosis UK.

Potential participants who have developed an acute CAT within 14 days, received <72 hours of anticoagulation for index CAT and have platelet count <50×10⁹/L are randomized to one of two study arms and followed up for 30 +/-3 days:

- 1) Study arm without platelet transfusion:
 - I. Platelet count 25-50×10⁹/L: 50% dose low-molecular-weight heparins (LMWH).
 - II. Platelet count <25×10⁹/L: hold anticoagulation.
- 2) Study arm with platelet transfusion:
 - I. Pre-transfusion platelet count 25-50×10⁹/L: 100% dose LMWH after one adult unit of platelet transfusion.
 - II. Pre-transfusion platelet count <25×10⁹/L: 50% dose LMWH after one adult unit of platelet transfusion.

Recruitment has begun for the feasibility phase of the study in Canada, with the aim of recruiting 50 patients internationally. The pilot trial is important to assess the feasibility and potential barriers to patient recruitment in this challenging area of study. It will allow assumptions about key parameters to be tested/validated and hence influence the study design for a future full-scale definitive trial. This is especially important in this patient population with a high risk of complications and where clinicians may have uncertainties in equipoise for recruitment to follow a protocol. Designing a definitive study that is pragmatic and provides important data to guide clinical practice is a major endeavor and will be best accomplished by international collaboration. Definitive studies also need to consider cost-effectiveness, given, for example, that more aggressive platelet transfusions also require more intense resource allocation.

The aim is that the full-scale trial will define the standard of

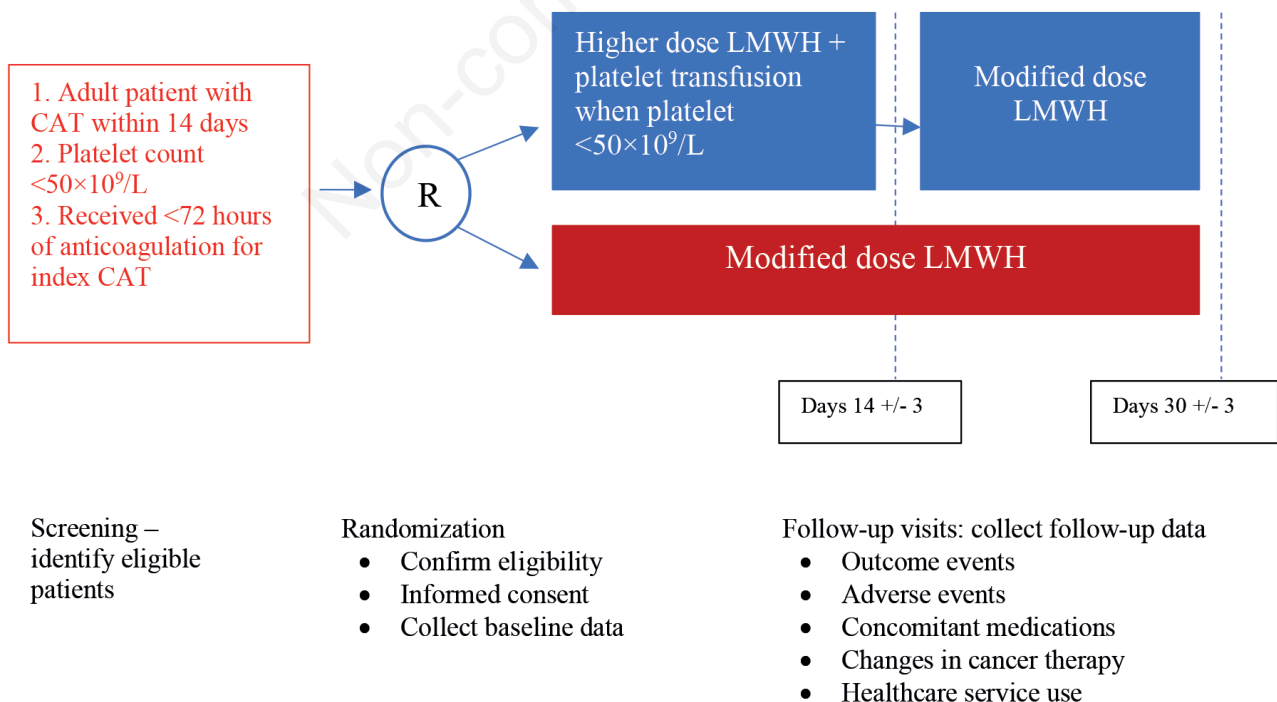


Figure 1. Study design of START trial. CAT, cancer-associated thrombosis; LMWH, low molecular weight heparin.

care for the management of patients with CAT and thrombocytopenia when treated with LMWH. As this is a patient group with high bleeding risk, future studies will then center around comparison of this newly defined standard of care with the use of alternative anticoagulants.

In conclusion, patients with CAT and thrombocytopenia are at high risk of both bleeding and thrombosis. Identification of the optimal management strategy is urgently needed which can best be established by the conduct of RCTs.

References

- Liebman HA. Thrombocytopenia in cancer patients. *Thromb Res* 2014;133:S63-9.
- Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med* 2010;362:600-13.
- Samuelson Bannow BR, Lee AYY, Khorana AA, et al. Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: a systematic review. *Res Pract Thromb Haemost* 2018;2:664-9.
- Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *Br J Cancer* 2016;115:1147-55.
- Falanga A, Marchetti M. Cancer-associated thrombosis: enhanced awareness and pathophysiologic complexity. *J Thromb Haemost* 2023;21:1397-408.
- Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood* 2021;137:1959-69.
- Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol* 2019;20:e566-81.
- Hsu C, Patell R, Zwicker JI. The prevalence of thrombocytopenia in patients with acute cancer-associated thrombosis. *Blood Adv* 2023;7:4721-7.
- Pegourie B, Karlin L, Benboubker L, et al. Apixaban for the prevention of thromboembolism in immunomodulatory-treated myeloma patients: Myelaxat, a phase 2 pilot study. *Am J Hematol* 2019;94:635-40.
- De Stefano V, Sorà F, Rossi E, et al. The risk of thrombosis in patients with acute leukemia: Occurrence of thrombosis at diagnosis and during treatment. *J Thromb Haemost* 2005;3:1985-92.
- Kekre N, Connors JM. Venous thromboembolism incidence in hematologic malignancies. *Blood Rev* 2019;33:24-32.
- Gerber DE, Segal JB, Yair Levy M, et al. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. *Blood* 2008;112:504-10.
- Khorana A, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111:4902-7.
- Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica* 2019;104:1277-87.
- Wang TF, Carrier M, Carney BJ, et al. Anticoagulation management and related outcomes in patients with cancer-associated thrombosis and thrombocytopenia: a systematic review and meta-analysis. *Thromb Res* 2023;227:8-16.
- Sørensen HT, Mellekjær L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *New Eng J Med* 2000;343:1846-50.
- Cohen AT, Katholing A, Rietbrock S, et al. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer: a population-based cohort study. *Thromb Haemost* 2017;117:57-65.
- Samuelson Bannow BT, Lee A, Khorana AA, et al. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018;16:1246-9.
- Estcourt LJ, Birchall J, Allard S, et al. Guidelines for the Use of Platelet Transfusions A British Society for Haematology Guideline. Available from: https://b-s-h.org.uk/media/2641/besh_platelet_guideline_08_08_16_v2.pdf (cited 2023 Jun 15)
- Curley A, Stanworth SJ, Willoughby K, et al. Randomized Trial of platelet-transfusion thresholds in neonates. *New Eng J Med* 2019;380:242-51.
- Baharoglu MI, Cordonnier C, Salman RAS, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet* 2016;387:2605-13.
- Carrier M, Blais N, Crowther M, et al. Treatment algorithm in cancer-associated thrombosis: updated Canadian expert consensus. *Curr Oncol* 2021;28:5434-51.
- Carney BJ, Wang TF, Ren S, et al. Anticoagulation in cancer-associated thromboembolism with thrombocytopenia: a prospective, multicenter cohort study. *Blood Adv* 2021;5:5546-53.
- Booth S, Desborough M, Curry N, et al. Platelet transfusion and anticoagulation in hematological cancer-associated thrombosis and thrombocytopenia: The CAVEaT multicenter prospective cohort. *J Thromb Haemost* 2022;20:1830-8.