# The balance between hemorrhage and thrombosis in patients surviving spontaneous intracerebral bleeding: the nightmare of a neurologist

Alessandro Pezzini

Department of Medicine and Surgery, University of Parma; Stroke Care Program, Department of Emergency, Parma University Hospital, Parma, Italy

With approximately 3 million people worldwide affected each year and the highly associated mortality and morbidity,[1] intracerebral hemorrhage (ICH) is the stroke subtype with the most severe clinical consequences. This is mainly due, on the one hand, to the lack of specific acute treatments, as opposed to the ischemic counterpart of stroke, on the other hand, to the occurrence of further vascular events after the index bleeding. Contrary to what has traditionally been believed, emerging data suggest that patients with spontaneous ICH may be not only at risk for recurrent cerebral bleeding but also at a higher risk of arterial ischemic events than the general population.[2] The rates of ischemic stroke (IS) after ICH, in fact, have been reported to range between 1% and 6%, those of myocardial infarction up to 4%,[2,3] while the annual rate of overall major cardiovascular events (MACE) is between 7% and 19%.[4] Better secondary prevention of all MACE after ICH is, therefore, a crucial issue for clinicians. Notwithstanding, mainly because of concerns about ICH recurrence, recommendations on the use of antithrombotic medications for secondary prevention of arterial thrombotic events in these patients are still matter of debate, even in selected ICH subgroups, such as, for example, those with specific comorbid conditions, like atrial fibrillation (AF).[5] Stated another way, what, if any, antithrombotic secondary prevention therapy should be offered to ICH survivors is still a clinical dilemma.

The REstart or Stop Antithrombotics Randomized Trial (RESTART), a pilot study conducted at 122 hospitals in the United Kingdom, is the only RCT that compares starting *versus* avoiding long-term antiplatelet treatment after ICH.[6,7] RESTART's overall finding was that starting antiplatelet treatment after ICH was unlikely to increase the risk of recurrent events compared to antiplatelet avoidance over a median of 3.0 years of follow-up (HR 0.51; 95%CI 0.25-1.03; p=0.060), with no heterogeneity of the effects by ICH location (lobar ICH *versus* non-lobar ICH), time of randomization (earlier *versus* later than 10 to 11 weeks), co-existent AF and computed tomography/MRI brain imaging biomarkers [cerebral microbleeds or other markers of cerebral amyloid angiopathy (CAA), a vascular disorder characterized by β-amyloid deposition on the vessel wall and increased vascular fragility]. Although these overall effects are somewhat reassuring for clinicians about the use of antiplatelets after ICH, effects estimates are somewhat limited because of the relatively small sample size of this pilot RCT.

The decision to resume oral anticoagulant (OAC) therapy after ICH is even more challenging. Observational data suggest that resuming OAC is associated with reduced thromboembolic events and all-cause mortality without a significant increase of ICH recurrence, whilst there is some variation between individual studies.[8] The major drawback of these analyses, however, is inherent to the risk of selection bias because of their retrospective design. Patients who resumed anticoagulation were younger, with less severe ICH, a more favorable initial prognosis and underrepresentation of risk factors for bleeding (such as, for example, CAA) than those who did not re-initiate OAC treatment. To overcome these limitations, the Start or Stop Anticoagulants Randomized Trial (SoSTART) enrolled 203 patients with AF and a median $CHA_2DS_2$-VASc score of 4 either to restart or to avoid OAC a median of 115 (IQR, 49-265) days after OAC-ICH.[9] The study found no significant difference in recurrent ICH (HR 2.42; 95%CI 0.72-8.09; p=0.152) but higher rates of IS in the avoid group (17% *versus* 3%). Therefore, there is substantial agreement that OAC could be resumed safely in many patients following an OAC-ICH. Concerns may arise in case of ICH occurring in lobar location, which is known to be at a higher recurrence risk than deep hemorrhage. In this regard, some authors recommend that patients with probable CAA – which is responsible for most cases of lobar ICH – should not be re-anticoagulated. Furthermore, given the reduced risk of ICH associated with direct oral anticoagulants (DOACs) compared to warfarin, some consensus guidelines recommend that they should be the preferred anticoagulant class in ICH survivors. On this basis,

Correspondence: Alessandro Pezzini, Department of Medicine and Surgery, University of Parma; Stroke Care Program, Department of Emergency, Parma University Hospital, Parma, Italy
Tel: +39.0521.902565.
E-mail: alessandro.pezzini@unipr.it

Key words: intracerebral hemorrhage, thrombosis, antithrombotic.

Received: 25 July 2024.
Accepted: 25 July 2024.


*Bleeding, Thrombosis and Vascular Biology 2024; 3:151*
*doi:10.4081/btvb.2024.151*

patients who were previously taking warfarin should be switched to a DOAC following ICH. In patients with AF at a very high risk of rebleeding post-ICH, mechanical device therapies, such as left atrial appendage occlusion (LAAO), might be an alternative to resumption of anticoagulation. Finally, there is little agreement regarding the optimal time to resume OAC. The risk of re-bleeding is high soon after the index ICH and remains elevated for the first months before slowly declining. Accordingly, the 2020 European Society of Cardiology AF Guidelines recommend to re-initiate OAC 4 to 8 weeks after ICH provided the cause of hemorrhage is controlled.[10] The more recent 2022 American Heart Association/American Stroke Association spontaneous ICH guidelines are more conservative, suggesting a later and narrower timeframe of 7 to 8 weeks after the index cerebral bleeding.[5]

In conclusion, management of antithrombotic agents after ICH remains a challenge for clinicians. Antiplatelet agents are promising for reducing the high risk of MACE and their use after ICH may be reasonable in everyday clinical practice. Similarly, the decision to resume anticoagulation is likely appropriate in the majority of patients who do not have features of CAA, based on a lower risk of mortality and thromboembolism without a significant increased risk of recurrent bleeding. The optimal time should be in a time window of 7 to 14 days in patients where the thromboembolism risk outweighs the re-bleeding risk and between 6 and 8 weeks in patients where the risk of re-bleeding predominates. Robust indications will hopefully come from the large RCTs currently underway. Until then, multidisciplinary collaboration between vascular neurologists, cardiologists, neurosurgeons, hematologists, is needed to make individualized management decisions tailored to each patient's risk profile.

## References


1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:439-58.
2. Li L, Murthy SB. Cardiovascular events after intracerebral hemorrhage. Stroke 2022;53:2131-4.
3. Pezzini A, Iacoviello L, Di Castelnuovo A, et al. Long-term risks of arterial thrombosis after intracerebral hemorrhage: MUCH Italy. Stroke 2024;55:634-42.
4. Banerjee G, Wilson D, Ambler G, et al. CROMIS-2 collaborators. Longer term stroke risk in intracerebral hemorrhage survivors. J Neurol Neurosurg Psychiatry 2020;91:840-5.
5. Greenberg SM, Ziai WC, Cordonnier C, et al. American Heart Association/American Stroke Association. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: A guideline from the American Heart Association/American Stroke Association. Stroke 2022;53:e282-361.
6. Al-Shahi Salman R, Minks DP, Mitra D, et al. RESTART Collaboration. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral hemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. Lancet Neurol 2019;18:643-52.
7. Al-Shahi Salman R, Dennis MS, Sandercock PAG, et al. Effects of antiplatelet therapy after stroke caused by intracerebral hemorrhage: extended follow-up of the RESTART randomized clinical trial. JAMA Neurol 2021;78:1179-86.
8. El Naamani K, Abbas R, Ghanem M, et al. Resuming anticoagulants in patients with intracranial hemorrhage: a meta-analysis and literature review. Neurosurgery 2024;94:14-9.
9. SoSTART Collaboration. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial hemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. Lancet Neurol 2021;20:842-53.
10. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:4194.