Anticoagulation for Thromboprophylaxis in Patients with Intracerebral Hemorrhage: Less Room for Skepticism

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Thromb Haemost 2022;122:1071–1074.

Epidemiological data show that in patients with intracerebral hemorrhage (ICH) the occurrence of venous thromboembolism (VTE) is quite common[1]; some recent reports from the United States estimate that up to 3% of ICH patients develop deep vein thrombosis (DVT) or pulmonary embolism (PE),[2] while other data indicate that the prevalence of symptomatic VTE could rise up to 10% of patients, of which 80% are asymptomatic episodes.[1] Still, thromboprophylaxis with heparin (either low-molecular-weight heparin [LMWH] or unfractionated heparin [UFH]) is strongly underprescribed in ICH patients,[1,3] being prescribed in 8 to 17% of patients.[1,3] This is mainly driven by the fact that these patients are perceived to be of high risk for bleeding by the treating physicians, as well as the limited related evidence from randomized controlled trials which does not allow for high-quality strong clinical recommendations (►**Table 1**). The major guidelines that focus on the management of VTE risk or on the clinical management of patients with ICH generally provide weak recommendation with an overall low quality of evidence.[4–9] This is despite the intense interest into understanding the risk factors for bleeding (especially in high-risk patient groups,[10–12] the long-term risks of bleeding after discontinuing anticoagulation therapy,[13] and improved efforts at bleeding risk stratification and balancing the risk–benefits of reintroducing anticoagulation after a major bleeding event).[14,15]

In this issue of *Thrombosis and Haemostasis*, Chi and colleagues present a systematic review of the association between pharmacological thromboprophylaxis with LMWH or UFH and the risk of VTE in patients with ICH.[16] After a methodologically robust systematic search and study selection, the authors included 28 studies and a total of 3,697 hospitalized patients with ICH. The mean patient age ranged between 50 and 72 years. The prevalence of risk factors and comorbidities largely varied across studies. Among the studies which evaluated LMWH, dosing regimens ranged between 20 and 40 mg daily (equal to 1,900 and 9,500 IU daily, respectively), while among the studies evaluating UFH, doses varied between 5,000 IU/8 hours and 5,000 IU/12 hours. The outcomes assessed included DVT, PE, hematoma expansion or rebleeding, major disability, and mortality.[16]

The investigators show that the use of pharmacological thromboprophylaxis was associated with a significant reduction in the risk of DVT, both in fixed-effects model (risk reduction [RR]: 0.24, 95% confidence interval [CI]: 0.28–0.32) and in the random-effects model (RR: 0.27, 95% CI: 0.19–0.39). These estimates were corroborated by low grade of heterogeneity ($I^2 = 25\%$) and by a strict prediction interval (PI; 0.11–0.66), which is a statistical tool used to examine the possible variation of pooled estimates according to future studies performed in different clinical scenarios and with different clinical characteristics. Furthermore, pharmacological thromboprophylaxis (RR: 0.33, 95% CI: 0.19–0.57 for the fixed-effects model; RR: 0.37, 95% CI: 0.21–0.66 for the random-effects model) was associated with a lower risk of PE without any heterogeneity ($I^2 = 0\%$), with the PI substantially overlapping the estimates (CI: 0.20–0.69), strengthening the results of the meta-analysis.[16] Moreover, pharmacological thromboprophylaxis was not associated with increased risk for hematoma expansion or rebleeding (RR: 0.75, 95% CI: 0.48–1.18 for the fixed-effects model; RR: 0.80, 95% CI: 0.49–1.30 for the random-effects model), with

received
April 14, 2022
accepted
April 22, 2022
published online
June 28, 2022

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-1834-4923.
ISSN 0340-6245.

Table 1 Guideline recommendations regarding thromboprophylaxis in patients with intracerebral hemorrhage

Guideline	Year	Thromboprophylaxis recommended	Agent	Timing	Quality of evidence
ACCP[4]	2012	Yes[a]	LMWH/UFH	Not mentioned	Weak recommendation, low quality of evidence (Grade 2C)
ESO[5]	2014	No	–	–	No formal recommendation
AHA/ASA[6]	2015	Yes	LMWH/UFH	1–4 days	Class IIb, level of evidence B
NCS[7]	2016	Yes	LMWH/UFH	Within 2 days	Weak recommendation, low quality of evidence
ASH[8]	2018	Yes[a]	LMWH/UFH	Not mentioned	Strong recommendation, moderate certainty of evidence
HSFC[9]	2020	Yes	LMWH	After 2 days	Evidence level B

Abbreviations: ACCP, American College of Chest Physicians; AHA, American Heart Association; ASA, American Stroke Association; ASH, American Society of Hematology; ESO, European Stroke Organization; HSFC, Heart and Stroke Foundation of Canada; LMWH, low-molecular-weight heparin; NCS, Neurocritical Care Society; UFH, unfractionated heparin.
[a]Refers generically to critically ill patients and not specifically to intracerebral hemorrhage.

no heterogeneity ($I^2 = 0\%$) and overlapping PI. Also, a trend of reduced mortality was identified in patients treated with pharmacological thromboprophylaxis (RR: 0.82, 95% CI: 0.65–1.03 for fixed-effects model; RR: 0.83, 95% CI: 0.66–1.04 for the random-effects model; $I^2 = 0\%$; PI: 0.60–1.15). Lastly, the fixed-effects model showed a higher risk for developing major disability in patients treated with a pharmacological thromboprophylaxis (RR: 1.20, 95% CI: 1.04–1.38), but this estimate was based only on two studies, was characterized by a high degree of heterogeneity ($I^2 = 83\%$), and was not confirmed in the random-effects model analysis (RR: 1.02, 95% CI: 0.62–1.65).[16]

To further support their results, the investigators performed several subgroup analyses (according to study design, type of ICH and type of anticoagulant), which substantially confirmed the main estimates. As a notable exception, the authors found that in patients with spontaneous ICH, the effect of pharmacological thromboprophylaxis was not associated with a reduction in VTE risk; however, this was based on a limited number of studies. Also, the additional analyses showed that among randomized controlled trials, patients receiving LMWH/UFH were associated with a lower risk of hematoma expansion or rebleeding (RR: 0.53, 95% CI: 0.28–0.99; $I^2 = 0\%$; $p = 0.13$ for test for subgroup differences).[16] Finally, it is noted that there was a significant overall risk of bias for most of the studies enrolled, with eight studies being at high risk of bias.

The result of this meta-analysis adds some reassurance for the use of pharmacological thromboprophylaxis with LMWH/UFH in patients with ICH and increases its implementation in this patient group, given the low risk of DVT/PE, the trend in lower risk of death, and the absence of any major bleeding complication (hematoma expansion or rebleeding). Still, this conclusion needs to be further confirmed in future randomized trials. During the last 13 years, the use of direct oral anticoagulants (DOACs) has increased substantially and they largely replaced vitamin K antagonists as the treatment of choice for most indications for oral anticoagulation.[17–21] In the management of VTE in medically ill patients, while DOACs showed a consistent superiority over LMWH in the reduction of thromboembolic events, they were also associated with an increase in the risk of major bleeding.[22] Notwithstanding this, a deeper analysis regarding the balance between the number of fatal bleeding and fatal VTE events showed that the rate of fatal VTE is higher than the rate of fatal bleeding. Also, a cost-effectiveness analysis indicated that the use of DOACs for the prevention of VTE is cost-effective compared with the use of LMWH.[22] Interestingly, none of the studies that tested DOACs for this indication included patients with ICH, and three out of four of these studies listed ICH as an exclusion criteria.[22] In this context, DOACs could be a candidate anticoagulation strategy to be tested in patients with this specific clinical scenario in future trials.

Finally, these results have implications also for the wider population of patients who have an indication for oral anticoagulation, but at the same time, they are at increased risk of bleeding. Not infrequently, treating physicians are frequently skeptic and reluctant to prescribe anticoagulant drugs in such patients and consequently, these patients are less likely to be treated with anticoagulants, as it is the case with atrial fibrillation patients who have a major bleeding during oral anticoagulant treatment or with significant liver disease.[23–26] In these settings, the available evidence suggests an overall significant clinical benefit if treated with oral anticoagulants.[25,26] The study by Chi and colleagues further strengthens this argument and underlines that bleeding risk should not be a reason to withhold anticoagulation, but it should rather serve as a flag for better control of bleeding risk factors.

In conclusion, in this large systematic review and meta-analysis, the authors demonstrated that a pharmacological thromboprophylaxis with LMWH or UFH is associated with a significant reduction in VTE (►**Fig. 1**). While this study further underlines that higher bleeding risk should not be a reason to withhold anticoagulant treatment, further

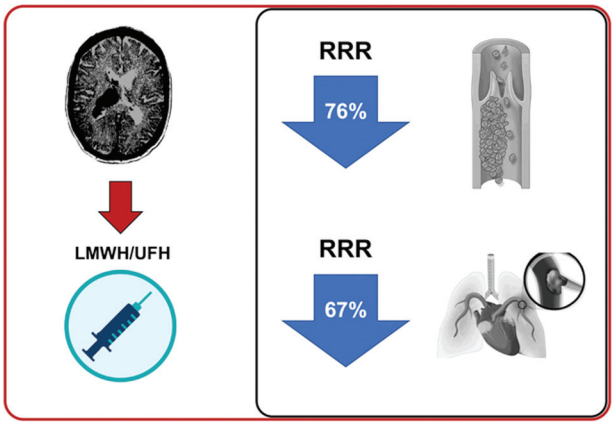

Fig. 1 Risk reduction of venous thromboembolic events in patients with intracerebral hemorrhage receiving thromboprophylaxis. LMWH, low-molecular-weight heparin; RRR, relative risk reduction; UFH, unfractionated heparin.

studies are still needed to support stronger recommendations and to further evaluate the use of other anticoagulant drugs (i.e., DOACs) in these patients. Other considerations include better patient engagement and highlighting the need for shared decision-making.[27]

Conflict of Interest
None declared.

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