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Editorial

Assessment of in-hospital bleeding risk in pulmonary embolism: What's the score? And what do I do with it?

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The evaluation of bleeding risk is an imperative step when initiating anticoagulant therapy in the setting of venous thrombo-embolic disease. The risk of recurrent venous thrombo-embolism (VTE) in the absence of anticoagulation should be weighed against the risk of bleeding events that may occur under anticoagulant therapy. This may lead to vena cava filter insertion in patients with acute pulmonary embolism (PE) and absolute contraindications to anticoagulation, or conversely, to initiation of long-term therapy beyond 3 to 6 months in patients at high risk of recurrence combined with low bleeding risk [1].

The annual incidence of major bleeding under vitamin K antagonists is around 2 to 3% in observational cohort studies, and 1 to 2% in randomized trials [2]. More strikingly, cohort studies report that the mortality linked to these major bleeding events is 20%, i.e. twice as high as the rate of death from recurrent PE. By way of comparison, the annual incidence of major bleeding with direct oral anticoagulants (DOACs) is around 0.5 to 1% in randomized controlled trials, and associated with a case fatality rate of 10%. The predictors of long-term bleeding complications are now well identified, regardless of the pathology considered (atrial fibrillation or VTE). Several predictive scores have been developed, mainly in patients with atrial fibrillation treated with vitamin K antagonists, but their validity and utility in patients treated for VTE have not been established [3,4]. To meet this need, the ACCP established a list of 18 variables identified from cohort studies, and any patient presenting at least two of those 18 variables is considered to be at high risk of bleeding complication [5]. Interestingly, although the risk of bleeding is increased within the first few weeks of treatment, most of these scores focused on the risk associated with long-term treatment.

Against this background, Kresoja and colleagues report in this issue [6] on the external validation and in-hospital prognostic impact of the VTE-BLEED score in a real world cohort of patients with PE. The VTE-BLEED score was developed from the dabigatran arms of the pooled RE-COVER sister studies, and validated in the HOKUSAI-VTE study [7,8], where patients at high bleeding risk, defined as a VTE-BLEED score ≥2, had a fourfold increase in the risk of bleeding during the chronic phase of treatment (>30 days). The present study by Kresoja and colleagues confirms the validity of the VTE-BLEED score for the prediction of in-hospital major bleeding. Among the 58% of patients with a VTE-BLEED score ≥2, there was a 3.7-fold increase in the risk of in-hospital major bleeding. In addition, in-hospital bleeds had a major impact on mortality, with a 7.6-fold increase in the risk of early death and 3.2 fold increase in the risk of one-year mortality. This alone is sufficient motivation for the development of scores to identify patients at high bleeding risk. Indeed, it is the key justification, given the current trend towards a multiplicity of scores in cardiology, many of which are often complex, rarely validated and never actually used.

Despite its attractiveness, the VTE-BLEED score nonetheless suffers from certain limitations. Some of its constituent components are likely less impactful at the in-hospital phase than on long-term follow-up. This is particularly true for males with uncontrolled hypertension, history of bleeding and age ≥60 years, in contrast to anaemia, active cancer and renal dysfunction, whose impact on the risk of in-hospital major bleeding is undeniable. This clearly underscores the fact that no score can claim to enjoy optimal sensitivity. Furthermore, findings might be affected by the fact that initial anticoagulant regimens were not standardized and therapeutic decision-making was at the discretion of the treating physician. Only 3% of patients were initially treated with DOACs and only 26% switched to DOACs during the in-hospital stay. This indicates that the validation of the VTE-BLEED score regarding the prediction of in-hospital bleeds and evaluation of their impact was driven mainly by patients not initially treated with DOACs. It is probable that the type of anticoagulant did not affect the overall results, but we cannot rule out the possibility that certain variables of the score have less impact in a patient treated with DOACs. There is a gap in the

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knowledge in this field that warrants further studies, especially in the current era of widespread DOAC use as first-line therapy.

The question that remains unresolved is how we should treat a patient with a VTE-BLEED score ≥2. Clearly, such a patient will not be a candidate for long-term anticoagulant therapy beyond 3 to 6 months. Yet, it is unclear what therapeutic alternatives can be proposed, or what precautions can be taken during the acute in-hospital phase to reduce the haemorrhagic risk, while at the same time, achieving sufficient antithrombotic effect. It is noteworthy that of the patients in this study who were treated with DOACs, or who switched to DOACs, none suffered from major bleeding. This opens perspectives for the wider use of DOACs in patients with a VTE-BLEED score ≥2, pending confirmation from randomized trials that such a strategy is safe as well as effective. Unfortunately, although a randomized study demonstrating that the use of VTE-BLEED score leads to improved clinical outcomes compared to usual care would be the true test of its value, it is unlikely that such a study will ever be conducted. Kresoja and colleagues have to be congratulated for having performed this external validation, which extends the applicability of the VTE-BLEED score to the hospital phase. Indeed, guidelines on how to develop and test a prediction model all stress the importance of external validation, as prediction models usually perform less well in new subjects. As the quantum physicist and Nobel Prize winner Niels Bohr correctly remarked, “prediction is very difficult, especially if it's about future”.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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