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Commentary

Preventing venous thromboembolism without causing harm

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The approach to venous thromboembolism (VTE) in non-surgical patients in the US has evolved over the last twenty years. The focus from 2000 to 2010 was on increasing awareness and ensuring physicians provided prophylaxis. Post 2011, after two pivotal studies changed what we knew about the risk-benefit tradeoff [1,2], we switched to personalised care using modeling to decide which patients should receive chemoprophylaxis. Since then we've struggled to find the best model, or risk score, for precisely assessing both bleeding and clotting risk.

There are a number of scores for calculating VTE risk for a hospitalised medical patient, but fewer available to estimate bleeding risk. The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) bleeding risk score (BRS) was specifically designed to help physicians balance VTE with bleeding risk for non-surgical patients hospitalized for more than two days. The original derivation study included 10 866 patients enrolled from predominantly for-profit hospitals across 12 countries and five continents [3]. Although well done, it has a few limitations. First, it is observational, so the BRS did not determine who got chemoprophylaxis and who did not. A large portion of the population did (48% chemoprophylaxis and 9% mechanical), creating confounding by indication as an informal clinical assessment for bleeding risk likely altered prophylaxis decisions.

Second, hospitalized medical patients are by nature heterogeneous, and the IMPROVE cohort is no exception. All models require external validation to prove their validity. When the characteristics of the derivation population are likely to differ from the patients the model is applied to, as is the case for any model designed for use in medical patients, external validation takes on added importance. Although IMPROVE has already been externally validated for hospitalised medical populations in the US [4,5], its performance across countries and co-morbidities would benefit from additional study.

Enter the recent article published by Zhang and colleagues in *The Lancet Regional Health – Western Pacific* [6]. The authors used data from DissolVE-2, a retrospective study that included patients from 60 teaching hospitals across 44 cities in China, to validate the IMPROVE BRS. The Zhang study includes 5076 hospitalized medical patients, after excluding 1547 with missing values for INR, platelet count, or GFR. The data collection was comprehensive, which allowed the authors to re-create and test the IMPROVE BRS in the DissolVE-2 population. The authors found an area under the receiver operating characteristic curve (AUROC) of 0•73 for clinically relevant bleeding (CRB). This is a higher AUROC compared to the existing external validation studies by Rosenberg and Hostler, which were 0•63 and 0•64 respectively.

The Zhang study is important for several reasons. First, it helps address the relationship between the IMPROVE BRS and the presence of chemical prophylaxis, because prophylaxis rates in the population studied were quite low (7•8%) compared to the original IMPROVE cohort (48%) and the two validation studies (82% and 80%). This helps reduce the confounding by indication that limited interpretation of previous studies. It shows in the absence of prophylaxis the IMPROVE BRS performs well.

It also provides external validation that for the reasons cited above, is critically important. The IMPROVE BRS has never been studied in a Chinese population, and the Zhang study reveals reasons it might perform differently than in Western countries. There are differences in age ranges, cancer rates, weight, and duration of hospitalization between the IMPROVE BRS derivation and Zhang studies, with likely unmeasured effects from comparing for-profit versus teaching hospitals.

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Next up for the Chinese investigators will be figuring out how to increase prophylaxis rates. The authors hypothesize that failure to provide chemoprophylaxis is related to fear of causing bleeding. If this is truly the case, the Zhang study could have a huge impact on prophylaxis rates in China. If there are other barriers, asking Chinese physicians to apply a complicated BRS like IMPROVE to every hospitalized medical patient may not have the desired effect. They may want to start with proven methods for increasing prophylaxis rates, like electronic reminders, chart audits and feedback, and local hospital champions [7,8].

Next up for the IMPROVE BRS is an intervention study. We need a prospective trial where the intervention arm protocolizes use of the IMPROVE BRS and a VTE risk score to decide whether chemoprophylaxis is indicated. The control arm would be usual care, and outcomes would be VTE and bleeding events during hospitalization. If the intervention arm can reduce VTE without increasing bleeding, we will know with certainty that risk scores improve outcomes. Such a trial will be large and expensive, so it may take a while to complete. In the meantime, the Zhang study significantly increases my confidence that the IPROVE BRS predicts clinically important bleeding events in acutely hospitalized medical patients.

Declaration of Competing Interest

No conflict of interest.

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