

# Refining Risk Prediction for Recurrent Venous Thromboembolism: Can We Do Better?

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Anticoagulation is effective in preventing and treating recurrent venous thromboembolism (VTE), but it causes bleeding.<sup>1–5</sup> Whether anticoagulation is stopped or continued longer term in patients with VTE depends on the trade-off between its benefit (reduction in VTE) and harm (increase in bleeding).<sup>6</sup> Many patients remain at risk of VTE recurrence after completing 3 months of anticoagulation for an acute episode of VTE and could benefit from indefinite anticoagulation, but identifying those patients remains challenging because of the inability to predict individual VTE and bleeding risks accurately.

The current management paradigm dichotomizes VTE as provoked or unprovoked (►Fig. 1A) because in general, compared with patients with a provoked VTE, those with an unprovoked event have a higher risk of VTE recurrence.<sup>7</sup> Accordingly, anticoagulation is stopped after 3 months in patients with provoked VTE and continued in those with unprovoked VTE or those with cancer-associated VTE in the absence of bleeding contraindication and after a discussion of risk-benefit.<sup>8</sup> Such an approach is useful but may be too simplistic, because it fails to recognize that some patients with provoked VTE remain at high risk of VTE recurrence and that some with unprovoked events have a low risk of recurrence (►Fig. 1B). Consequently, there is a need for better VTE risk prediction tools to guide clinical decision about the optimal duration of anticoagulation in patients with an incident VTE (►Fig. 1C).

To enhance VTE risk prediction beyond the current approach, Albertsen and colleagues modeled the risk of VTE recurrence in the Danish nationwide registries that included 11,519 patients who completed anticoagulation therapy for an index VTE diagnosed between 2012 and 2017 and who were followed for up to 2 years. In contrast to most previously developed VTE risk prediction models, which have typically excluded provoked VTE, the investigators included all VTE, irrespective of the presence of provoking factors.<sup>9</sup> Notable exclusions include the need for long-term antico-

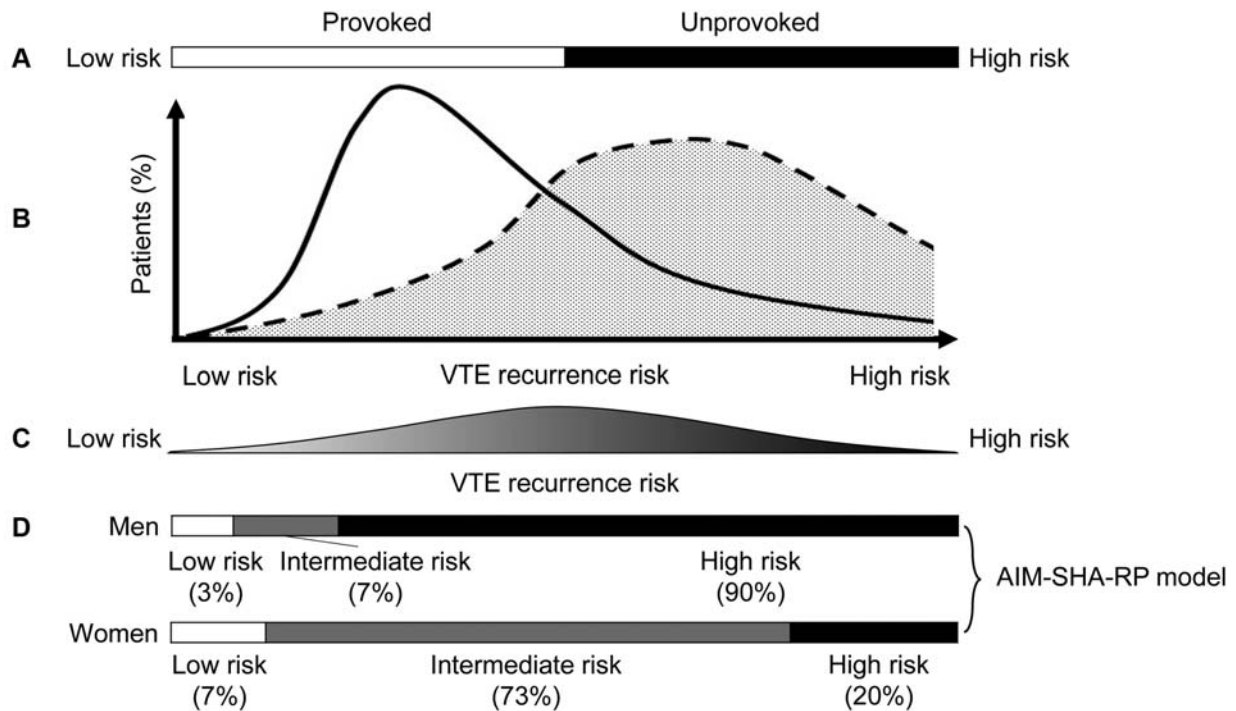
agulation (such as in patients with prevalent cancer, myeloproliferative disorders, or atrial fibrillation). Using a Cox regression model and a backward selection process, they derived and internally validated a sex-specific VTE risk prediction model—named AIM-SHA-RP—consisting of eight predictive clinical variables. They found Age, Incident pulmonary embolism, and Major surgery to be predictive in both sexes. Statin use, Hear disease, and Antiplatelet use were predictive in men only, whereas Renal disease and Pneumonia/sepsis were predictive in women only (►Supplementary Table S1 [available in the online version]). The inclusion of these variables has face validity since each has been independently associated with recurrent VTE in previous studies.<sup>10</sup> To develop the AIM-SHA-RP scoring system, each variable was assigned a weighted score based on its hazard ratio for recurrent VTE. Importantly, their model stratified both women and men into three distinct VTE risk categories and was able to identify female as well as male patients with low annual risk of VTE recurrence <5%, who may be able to stop anticoagulation.<sup>11</sup> For men, 3% were categorized as low risk, which corresponded to a VTE recurrence rate of 2.34 per 100 person-years, 7% were at intermediate risk with a rate of 3.17 per 100 person-years, and the remaining 90% were at high risk with a rate of 7.43 per 100 person-years. Similarly, for women, 7, 73, and 20% could be categorized as low, intermediate, and high risk of VTE recurrence, respectively (►Fig. 1D), and their corresponding rates were 2.07, 4.34, and 9.01 per 100 person-years, respectively.

To refine risk stratification, others have taken various approaches. Expert clinicians use clinical judgment and consider the presence of validated risk factors on top of the unprovoked/provoked dichotomy when making decision on the duration of anticoagulation,<sup>12</sup> but unlike a standardized risk prediction model like AIM-SHA-RP, such an approach may be less reproducible if used by nonexpert. To

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**Fig. 1** Conceptual figures describing risk of VTE recurrence. (A) VTE recurrence risk in patients stratified as provoked versus unprovoked; (B) expected distribution of VTE recurrence risk in patients with provoked or unprovoked (shadow) VTE; (C) Expected distribution of the risk of recurrence in patients with VTE; and (D) three tiered risk categories (low, intermediate, and high with proportion of patients in each category [%]) in male and female patients as stratified by AIM-SHA-RP model. VTE, venous thromboembolism.

standardize the approach, other investigators have previously developed and (variably) validated several VTE risk prediction tools, but none of the 10 or so prediction models developed have gained much traction with guidelines (► **Supplementary Table S1** [available in the online version]). Of these, the Vienna,<sup>13</sup> HERDOO2,<sup>14</sup> and DASH prediction models<sup>15</sup> have been the most studied. Unlike the AIM-SHA-RP model, all three use a combination of clinical variables and D-dimer levels to risk-stratify patients, and all three were developed and validated in an exclusively unprovoked VTE population. Consequently, the AIM-SHA-RP is a simpler tool that can be applied to a wider VTE population since it was derived from an all-comer VTE population, much like the recent Leiden Thrombosis Recurrence Risk Prediction (L-TRRiP) models.<sup>16</sup> Four L-TRRiP models were recently derived from the Multiple Environment and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) study that included 3,750 patients with incident VTE, and were externally validated in another 923 patients. In general, models combining clinical variables with biomarkers have better discriminative power (C-statistics from 0.69 to 0.73) than those based on clinical variables alone, but the improvement in performance with a more complex model needs to be balanced with the ease of implementation in routine clinical practice.<sup>16</sup>

The key strength of the study by Albertsen and colleagues is the large and all-VTE inclusive population ( $n = 11,519$ ) from which the AIM-SHA-RP was derived and validated. Compared with existing prediction rules, the AIM-SHA-RP score has several strengths. First, like the L-TRRiP,<sup>16</sup> the AIM-

SHA-RP score can be applied to all-comers and be used to risk stratify both provoked and unprovoked VTE. Consequently, it refines VTE risk prediction across a broader population. Second, its strength resides in its simplicity because it estimates risk from easily accessible clinical variables and does not depend on the measurement of biomarkers. Third, the AIM-SHA-RP score was able to categorize women as well as men in low, intermediate, and high-risk categories and therefore is expected to be a clinically useful score for both sexes pending validation (c-statistics 0.62 for women and 0.56 for men). Several limitations, of which some were acknowledged by the authors, include (1) the potential for case ascertainment bias and missed diagnoses because of the use of ICD-10 and ATC codes to identify VTE, (2) the inability to ascertain fatal pulmonary embolism in those who died, and (3) the lack of external validation.

How will this study affect clinical practice? The current study shows that given a large enough database, it is possible to develop better models and refine VTE risk prediction using easily accessible clinical variables. Perhaps, the main obstacles to implementation of this prediction tool in clinical practice are (1) the lack of external validation, (2) the lack of a prospective clinical management study, and (3) the lack of explicit information about the risk threshold to guide the decision to continue or stop anticoagulation. The last point is important because only 4.7% of patients had low-risk AIM-SHA-RP scores, and therefore most patients are considered non-low risk and would have to continue anticoagulation. However, even patients with intermediate AIM-SHA-RP risk score have annual recurrence risk <5% in whom stopping

anticoagulation could also be considered.<sup>11</sup> Consequently, more work remains to be done to fine tune and validate the AIM-SHA-RP prediction tool before it can be implemented and used in clinical practice.

What else remains to be done? In addition to VTE risk, evaluation of bleeding risk is also important. Compared with recurrent VTE, the case-fatality of major bleeding due to anticoagulation is approximately two- to threefold higher.<sup>17</sup> Therefore, the development of bleeding risk prediction model and its integration in the trade-off could be the next major steps to improve decision-making about the optimal duration of anticoagulation. So far, bleeding models are lagging behind, but the recent development of the VTE-BLEED score is promising as it may differentiate patients with low (2.8% within in 6-month follow-up) from those at high risk of bleeding (12.6% within in 6-month follow-up).<sup>18,19</sup> In addition, cost-effectiveness,<sup>20</sup> patient preferences,<sup>21</sup> and the availability of the direct oral anticoagulants—which are safer and more convenient than vitamin K antagonists—are other important considerations when making decisions for individuals, but so far, there are no parsimonious models that integrate all those considerations. Finally, many thromboembolism and bleeding risk prediction rules focus on clinical factors or biomarkers determined as a “one off” assessment at baseline and events assessed many years later. In reality, risk assessment is a dynamic process because the risk changes with aging and incident risk factors. An unmet need is how to factor in risk changes over time to facilitate decision-making.

In summary, the optimal duration of anticoagulation depends on the clinician’s and patient’s risk-benefit trade off. Any approaches that refine VTE and bleeding risk prediction is expected to improve our ability to make better decisions for patients. Like L-TRRiP and other previous prediction rules,<sup>15</sup> AIM-SHA-RP has the potential to improve clinical outcomes of patients with VTE, but more work is required to examine its clinical utility.

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