COMMENTARY

A need to refine venous thromboembolism risk assessment: the challenge of optimizing patient selection for thromboprophylaxis among hospitalized adults

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The term prophylaxis combines the prefix "pro," meaning before; "phylax," meaning guard; and the suffix "sis," indicating a process or action [1]. Accordingly, thromboprophylaxis is the process of guarding patients from venous thromboembolic disease (VTE), a long-recognized complication of hospitalization that millions of patients are at risk for each year. For clinicians caring for hospitalized adults, serving as such a guard for their patients is not an easy task, given that broadly applied thromboprophylaxis may do little to impact overall rates of VTE [2,3].

Despite years of promoting aggressive VTE prophylaxis in hospitalized medical patients, providing thromboprophylaxis for patients at low risk could logically result in several negative outcomes: 1) increased costs for the drug and labor to administer it, 2) increased patient discomfort when using parenteral anticoagulants, 3) increased risk of bleeding, or with heparin products, complications like heparin-induced thrombocytopenia, and 4) administration of prophylaxis unnecessarily could inadvertently delay or complicate some higher risk inpatient surgeries or procedures.

Efforts to prevent venous thromboembolism have improved over time, but recent American Society of Hematology Guidelines note "there is low certainty in the evidence for a net health benefit from using any parenteral anticoagulant in acutely ill medical patients" [4]. Improved risk assessment for the competing risks of both bleeding and thrombosis could be a promising way to optimize thromboprophylaxis strategies (Figure). In fact, guidelines encourage the use of VTE and bleeding risk assessments as part of shared clinical decision-making for prophylaxis [4]. Limitations to this approach include that these risks are often dynamic throughout hospitalization and available

risk assessment models (RAMs) have not been robustly demonstrated to improve outcomes.

Recently in *RPTH*, Kocher et al. [5] reported on a prospective cohort study of 1,352 acutely ill hospitalized medical patients from 3 Swiss university hospitals. After applying 4 validated VTE RAMs, they report a concordant high-risk classification in only 25% of patients and 26% concordance in those classified as having low risk. Clinically, 37% to 41% of high-risk patients as predicted by RAMs did not receive prophylaxis, demonstrating a significant level of underprophylaxis. Additionally, 37% to 48% of RAM-classified low-risk patients received prophylaxis that appeared unwarranted, indicating a similarly high rate of overprophylaxis. Moreover, the present study showed the incidence of VTE was not clearly higher regardless of patient risk or whether prophylaxis was overused, underused, or appropriately prescribed, irrespective of the RAM used. The study findings underscore the need to 1) improve risk stratification, 2) study how risk-adapted management impacts clinically relevant outcomes, and 3) determine how to best implement prophylaxis recommendations, ideally using a process that facilitates shared decision-making.

Inappropriate VTE prophylaxis has been demonstrated in other studies, including a large prospective dataset of hospitalized medical patients showing an underprophylaxis rate of 22% and a staggering excess prophylaxis rate of 65.3% [6]. The problem of variable guidance on how to implement RAMs in clinical practice is further compounded by the RAMs themselves. Popular RAMs, such as the Padua score and the Geneva score, were derived based on expert opinion and literature review. They were studied in populations that included patients already receiving thromboprophylaxis [7]. Their predictive accuracy is
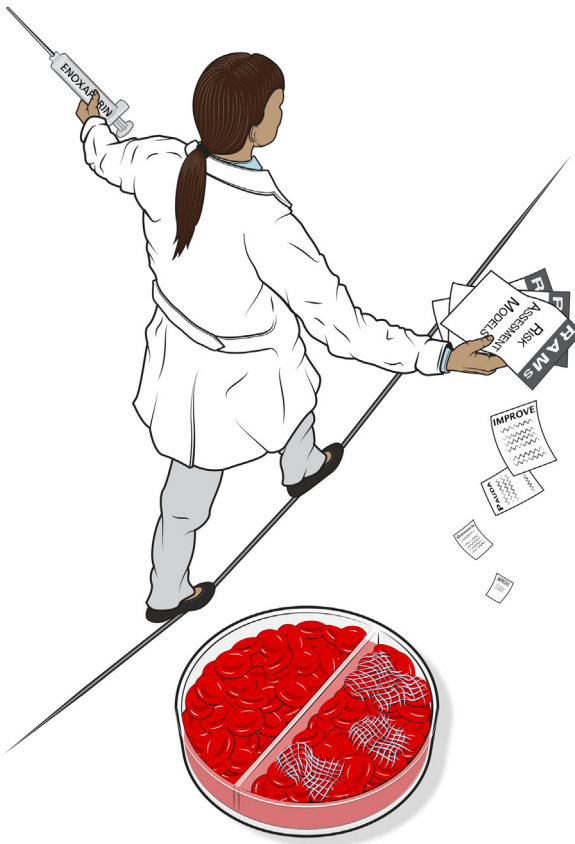
FIGURE This conceptual illustration is meant to depict the challenge of balancing the competing risks of bleeding and thrombosis when making decisions about venous thromboembolism prophylaxis. These decisions are often guided by risk assessment models that may inconsistently categorize patient risk. Overprophylaxis of patients at low risk and underprophylaxis of patients at high risk is a continued clinical challenge.

modest, they can be cumbersome to use, and important subgroups may be underrepresented [7–10]. Considering the limitations of these tools, it is not surprising that the number of patients classified as high-risk varied across RAMs in the present study [5]. However, the magnitude of difference between high- and low-risk categories (36%) based on RAM used seems to suggest that continued improvements in these models should be a priority.

Unfortunately prophylaxis decisions can still be challenging, even if using one of over a dozen RAMs available to guide risk-adapted prophylaxis decisions [11]. The operationalization and definition of VTE risk factors used in RAMs, like immobility, is variable [12]. Furthermore, what constitutes "adequate," "appropriate," "overuse," and "underuse" of prophylaxis is not broadly agreed upon [7]. While guidelines suggest VTE risk assessment upon hospital admission with provision of risk-adapted prophylaxis, they are heterogeneous in their suggestions, potentially owing to variation in the trial data upon which they are based [7].

Despite concerns about overuse, it is important to consider that VTE prophylaxis is generally safe and cost effective [13]. Despite the observed over and underuse of prophylaxis in the current study,

clinical outcomes were similar between the groups. Patients for whom prophylaxis was "underutilized" had a significantly higher rate of clinically non-relevant bleeding when the IMPROVE score was used, and while not statistically significant, the underuse category as a whole trended toward higher bleeding event rates [5]. Improving "appropriate" VTE prophylaxis would therefore likely further magnify these differences. This may be because thrombosis and bleeding share several common risk factors [14,15], so patients with high thrombotic risk are also at high risk for bleeding. As the authors note, it is also possible that a clinical bleeding risk assessment prompted the high rates of underuse [5]. Overuse of prophylaxis was notably not associated with increased bleeding, likely reflecting the safety of these medications when managed by appropriately trained providers. About 9% of patients had a contraindication to anticoagulation and with even some of these patients receiving pharmacologic VTE prophylaxis, there was not a clear increase in bleeding. This seems to emphasize that 1) RAMs should account for both bleeding and thrombotic risk to be maximally effective, and 2) prophylaxis is generally safe and until better data are available; it might be best to favor overuse when there is clinical equipoise.

The Call to Action by the American Heart Association in 2020 outlined policy steps to decrease VTE rates in hospitalized patients by 20% by 2030 [13]. The extent of progress over the past 3 years toward this goal is uncertain. In the current study, underuse of prophylaxis of VTE was not associated with a significant increase in thrombosis rates, but the study was likely underpowered for this. Optimistically, further advancements in risk prediction [11] will identify a set of variables that are readily available on hospital admission or dynamically assessed throughout a hospital stay that will allow VTE prevention without an increase in adverse bleeding outcomes. Recently, artificial intelligence has been studied as a method of VTE risk prediction and diagnosis with high sensitivity, specificity, and area under the receiver operating characteristic curve [16]. Although promising, it is unknown if artificial intelligence strategies will improve VTE risk prediction, prophylaxis, and clinical outcomes. Given patient diversity, complexity, and day-to-day variability, the problem of under and overprophylaxis will likely remain unless there are substantial advances in RAMs.

In addition to targeting improvements at the provider level through improved implementation of thromboprophylaxis [17], more effective RAMs, and standardization of definitions of success, it is probable that a more multi-level effort will prove valuable. For example, Haut et al. [18] showed that targeted patient education could significantly reduce rates of non-administration of VTE prophylaxis. With the long-term goal of reducing the incidence of VTE, especially fatal events, it seems feasible that greater patient awareness and engagement could be promising. Health-system level interventions to reduce patient immobility during hospitalization [19] and earlier patient recognition of VTE symptoms could also be high yield if successful implementation was possible. Finally, new antithrombotic agents with easier administration and a lower risk of bleeding, like the factor XI inhibitors, could significantly advance current treatment to prevent VTE [20]. Overall, the study by Kocher et al. [5] emphasizes

the limitations and heterogeneity of several available VTE RAMs, highlighting an opportunity to improve healthcare delivery.

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REFERENCES

[1] Merriam-Webster. (n.d.). Prophylaxis. In Merriam-Webster.com dictionary. from. https://www.merriam-webster.com/dictionary/prophylaxis [acessed September 17, 2023].

[2] Flanders SA, Greene MT, Grant P, Kaatz S, Paje D, Lee B, et al. Hospital performance for pharmacologic venous thromboembolism prophylaxis and rate of venous thromboembolism: a cohort study. *JAMA Intern Med*. 2014;174:1577–84.

[3] Mahan CE, Fisher MD, Mills RM, Fields LE, Stephenson JJ, Fu AC, et al. Thromboprophylaxis patterns, risk factors, and outcomes of care in the medically ill patient population. *Thromb Res*. 2013;132:520–6.

[4] Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2:3198–225.

[5] Kocher B, Darbellay Farhoumand P, Pulver D, Kopp B, Choffat D, Tritschler T, et al. Overuse and underuse of thromboprophylaxis in medical inpatients. *Res Pract Thromb Haemost*. 2023;7:102184.

[6] Grant PJ, Conlon A, Chopra V, Flanders SA. Use of venous thromboembolism prophylaxis in hospitalized patients. *JAMA Intern Med*. 2018;178:1122–4.

[7] Er C, Cohen AT. Limitations of venous thromboembolism risk assessment models in medical patients: response to "Unmet definitions in thromboprophylaxis for hospitalized medical patients: an appraisal for the need of recommendation.". *Res Pract Thromb Haemost*. 2023;7:100027.

[8] Pandor A, Tonkins M, Goodacre S, Sworn K, Clowes M, Griffin XL, et al. Risk assessment models for venous thromboembolism in hospitalised adult patients: a systematic review. *BMJ Open*. 2021;11: e045672.

[9] Forgo G, Micieli E, Ageno W, Castellucci LA, Cesarman-Maus G, Ddungu H, et al. An update on the global use of risk assessment models and thromboprophylaxis in hospitalized patients with medical illnesses from the World Thrombosis Day steering committee: Systematic review and meta-analysis. *J Thromb Haemost*. 2022;20:409–21.

[10] Greene MT, Spyropoulos AC, Chopra V, Grant PJ, Kaatz S, Bernstein SJ, et al. Validation of risk assessment models of venous thromboembolism in hospitalized medical patients. *Am J Med*. 2016;129:1001. e9–18.

[11] Darzi AJ, Repp AB, Spencer FA, Morsi RZ, Charide R, Etxeandia-Ikobaltzeta I, et al. Risk-assessment models for VTE and bleeding in hospitalized medical patients: an overview of systematic reviews. *Blood Adv*. 2020;4:4929–44.

[12] Ávila Ferreira B, de Bastos M, Rezende SM. Unmet definitions in thromboprophylaxis for hospitalized medical patients: an appraisal for the need of recommendation. *Res Pract Thromb Haemost*. 2022;6: e12827.

[13] Henke PK, Kahn SR, Pannucci CJ, Secemksy EA, Evans NS, Khorana AA, et al. Call to Action to Prevent Venous Thromboembolism in Hospitalized Patients: a policy statement from the American Heart Association. *Circulation*. 2020;141:e914–31.

[14] Natsuaki M, Morimoto T, Yamaji K, Watanabe H, Yoshikawa Y, Shiomi H, et al. Prediction of thrombotic and bleeding events after percutaneous coronary intervention: CREDO-Kyoto Thrombotic and Bleeding Risk Scores. *J Am Heart Assoc*. 2018;7:e008708.

[15] Klok FA, Huisman MV. How I assess and manage the risk of bleeding in patients treated for venous thromboembolism. *Blood*. 2020;135:724–34.

[16] Wang Q, Yuan L, Ding X, Zhou Z. Prediction and diagnosis of venous thromboembolism using artificial intelligence approaches: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2021;27:10760296211021162.

[17] Kahn SR, Morrison DR, Diendéré G, Piché A, Filion KB, Klil-Drori AJ, et al. Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism. *Cochrane Database Syst Rev*. 2018;4:CD008201.

[18] Haut ER, Aboagye JK, Shaffer DL, Wang J, Hobson DB, Yenokyan G, et al. Effect of real-time patient-centered education bundle on administration of venous thromboembolism prevention in hospitalized patients. *JAMA Netw Open*. 2018;1:e184741.

[19] Geelen SJ, Giele BM, Veenhof C, Nollet F, Engelbert RH, van der Schaaf M. The Better By Moving study: a multifaceted intervention to improve physical activity in adults during hospital stay. *Clin Rehabil*. 2022;36:1342–68.

[20] Poenou G, Dumitru Dumitru T, Lafaie L, Mismetti V, Heestermans M, et al. Factor XI inhibition for the prevention of venous thromboembolism: an update on current evidence and future perspectives. *Vasc Health Risk Manag*. 2022;18:359–73.