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COMMENTARY

Balancing the risks of recurrent venous thromboembolism and bleeding with extended anticoagulation: oh, for a crystal ball!

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Deciding the duration of anticoagulation after a first venous thromboembolism (VTE) event is an everyday scenario in the clinic but one that is fraught with uncertainties (Figure). After the initial period of anticoagulation, the decision to continue anticoagulation indefinitely involves weighing risk of VTE recurrence (if anticoagulation stops) with risk of bleeding (if anticoagulation continues). In Baglin et al.'s [1] landmark study, the presence or absence of provoking factors at presentation was a major determinant of risk of recurrence, with a 2-year incidence being higher after an unprovoked event (19.4%) than after surgery-related VTE (0%). Many current guidelines suggest extended anticoagulation after a first unprovoked event in patients at low risk of bleeding [2–5].

Contemporary systematic reviews and meta-analyses have helped shed further light on risk of recurrent VTE and bleeding after unprovoked VTE in those stopping and continuing anticoagulation. Risk of recurrent VTE after stopping anticoagulation after unprovoked VTE has been reported as 25% (95% CI, 21%-29%) at 5 years and 36% (95% CI, 28%-45%) at 10 years, with 4% (95% CI, 2%-6%) of events being fatal [6]. In another systematic review examining long-term bleeding risk in patients receiving extended anticoagulation, the incidence of major bleeding per 100 person-years was 1.74 (95% CI, 1.34-2.20) and 1.12 (95% CI, 0.72-1.62) events with vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), respectively [7]. The 5-year cumulative incidence of major bleeding was 6.3% (95% CI, 3.6%-10%) with VKAs (not reported after the first year with DOACs). The case-fatality rate was 8.3% (95% CI, 5.1%-12.2%) and 9.7% (95% CI, 3.2%-19.2%) in those receiving VKAs and DOACs, respectively.

A dichotomous approach pivoting on the absence/presence of a provoking factor still dominates clinical decision-making; there is also increasing awareness on the contribution of additional variables to the recurrence risk, such as sex, site of the VTE, and D-dimer [8]. Various prediction models have been devised, with 17 models to predict recurrence and 15 to predict bleeding [9]. A latest such model, the VTE-PREDICT score, estimates absolute risk of recurrent VTE and clinically relevant bleeding for patients with VTE without active cancer after the initial period of anticoagulation [10]. No distinction between provoked and unprovoked VTE is made at the outset. Like other models, there remain issues around predictive ability, validation, and generalizability. Due to these limitations, there remains a hesitancy among clinicians to use such models in routine care pathways.

The concept of shared decision-making has increasingly taken hold, and perhaps, it is in this setting that such predictive models might come into their own. Modeling outcomes might also help in decision-making, whether for an individual patient or to inform guideline development or health policy. A recent study featured in this journal sought to determine the optimal ratio of VTE recurrence risk reduction to increase risk of clinically relevant bleeding with extended anticoagulation in terms of impact on quality-adjusted life years (QALYs) [11]. The VTE-PREDICT score was used as the prediction tool to determine absolute risk reduction and increase in risk of clinically relevant bleeding with extended anticoagulation within 5 years. Data were simulated using the patient cohort from the Bleeding Risk Study [12]. They modeled the outcomes for 10,000 individuals, and while comparing the severity of bleeding and recurrent VTE, they found a ratio of 0.90 (95% CI, 0.51-3.40) to be optimal, with 99% of patients assigned extended anticoagulation, resulting in 93 (95% CI, −23 to 203) additional QALYs compared with the least favorable ratio (5.10, 0% extended anticoagulation). However, the difference in the optimal and least optimal ratios resulted in minimal health gains. They

FIGURE Deciding about the duration of anticoagulation after venous thromboembolism might be difficult. Shared decision-making considers the patient's perspective, predicted outcomes, and treatment burden.

conclude that the optimal ratio between reducing recurrence and bleeding remains uncertain.

The authors of the current study [11] are to be congratulated for their efforts in trying to establish the optimal ratio of recurrence to bleeding and the impact on quality of life. However, there was a wide CI around the point estimate for the optimal ratio, making it difficult to draw a meaningful conclusion. Providing 99% of all patients extended anticoagulation seems to deliver a gain of less than 1 day in perfect health. Could this departure from the perceived benefits of extended anticoagulation be attributed to the limitations of the modeling approach, including the population under study? The simulated population did not include risk factors for bleeding (patients with cancer, liver disease, or alcohol use), which may have led to a greater proportion of patients being assigned to receive anticoagulation. Eighty-nine percent cases of VTE were unprovoked, and only 36% of patients were women. As highlighted by the authors, the limitations of the VTE-PREDICT score are also inherited by the present study, with the exclusion of potentially relevant outcome predictors leading to a reduction in the heterogeneity of the predicted risks. Interestingly, the median untreated 5-year risk of recurrent VTE was 8.9% (IQR, 7.8%-9.6%), substantially lower than the widely quoted 25% 5-year risk of recurrence. The impact of the treatment effect might also be a factor. Their analysis is primarily based on a pooled estimate for the effect of extended anticoagulation using full-dose DOACs, and treatment effect estimates do not reflect the widespread use of reduced-dose DOACs in real-world practice.

Of note, another recent decision-analytical modeling study examined the cost-effectiveness of continuing vs stopping anticoagulation after the first unprovoked VTE and reported no increase in QALYs with indefinite anticoagulation at an increased financial cost [13]. This study found that for the average patient, extended anticoagulation was unlikely to result in a mortality benefit. This might be driven by the 2- to 3-fold higher case-fatality rate of major bleeding compared with recurrent VTE. Taken together, these modeling studies bring into sharp focus the need for accurate identification of patients for whom extended anticoagulation can be confidently recommended.

Where does this leave us when faced with a patient attending for a "duration review" or "shared decision-making" exercise? The data and how they are presented in the clinic are only half of the story. For the patient, the decision-making process involves much more than the statistics. Their perception of bleeding and thrombosis risk, their lived experience, and the lived experience of the people around them will shape how they approach the decision. Their beliefs, values, and concerns about effects on quality of life will be just as heterogeneous and "individualized" as the treatment decisions that are jointly agreed on [14,15]. The physical, psychological, and economic burdens of lifelong medication use should also not be forgotten. We agree with the authors that their study highlights how important shared decision-making is when considering whether to continue anticoagulation after initial VTE treatment. Modeling studies might help inform health policy and guidelines, but further implementation studies are necessary to reliably inform the patients regarding their risks. Studies centered on long-term use of reduced-dose DOACs are necessary, and the development of newer, safer anticoagulants might also hold an answer.

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REFERENCES

[1] Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet*. 2003;362:523–6.
[2] National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NICE Guideline 158; 2020. https://www.nice.org.uk/guidance/ng158. [accessed December 18, 2023]
[3] Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force

for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:543–603.

[4] Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4:4693–738.

[5] Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, et al. Antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel Report. *Chest*. 2021;160:e545–608. https://doi.org/10.1016/j.chest.2021.07.055

[6] Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. *BMJ*. 2019;366:l4363. https://doi.org/10.1136/bmj.l4363

[7] Khan F, Tritschler T, Kimpton M, Wells PS, Kearon C, Weitz JI, et al. Long-term risk for major bleeding during extended oral anticoagulant therapy for first unprovoked venous thromboembolism : a systematic review and meta-analysis. *Ann Intern Med*. 2021;174:1420–9.

[8] Kearon C, Kahn SR. Long-term treatment of venous thromboembolism. *Blood*. 2020;135:317–25.

[9] Burggraaf JLI, van Rein N, Klok FA, Cannegieter SC. How to predict recurrent venous thromboembolism and bleeding? A review of recent advances and their implications. *Pol Arch Intern Med*. 2023;133:16492. https://doi.org/10.20452/pamw.16492

[10] de Winter MA, Büller HR, Carrier M, Cohen AT, Hansen JB, Kaasjager KAH, et al. Recurrent venous thromboembolism and bleeding with extended anticoagulation: the VTE-PREDICT risk score. *Eur Heart J*. 2023;44:1231–44.

[11] de Winter MA, Thavorn K, Hageman SHJ, Nijkeuter M, Wells PS. Balancing risks of recurrent venous thromboembolism and bleeding with extended anticoagulation: a decision analysis. *Res Pract Thromb Haemost*. 2024;8:102274. https://doi.org/10.1016/j.rpth.2023.102274

[12] Wells PS, Tritschler T, Khan F, Anderson DR, Kahn SR, Lazo-Langner A, et al. Predicting major bleeding during extended anticoagulation for unprovoked or weakly provoked venous thromboembolism. *Blood Adv*. 2022;6:4605–16.

[13] Khan F, Coyle D, Thavorn K, van Katwyk S, Tritschler T, Hutton B, et al. Clinical benefits, harms, and cost-effectiveness of indefinite anticoagulant therapy for first unprovoked venous thromboembolism: a decision analytic modelling study. *Blood*. 2022;140:7858–9.

[14] Bartoli-Abdou JK, Patel JP, Xie R, Dzahini O, Vadher B, Brown A, et al. Associations between illness beliefs, medication beliefs, anticoagulation-related quality of life, and INR control: insights from the Switching Study. *Res Pract Thromb Haemost*. 2018;2:497–507.

[15] Fang MC, Go AS, Prasad PA, Hsu JW, Fan D, Portugal C, et al. Anticoagulant treatment satisfaction with warfarin and direct oral anticoagulants for venous thromboembolism. *J Thromb Thrombolysis*. 2021;52:1101–9.