COMMENTARY

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TO THE EDITOR:

# Commentary on the 2021 ASH Guidelines on use of anticoagulation in patients with COVID-19 being discharged from the hospital

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The COVID-19 pandemic has fundamentally changed the way we practice medicine, conduct clinical trials, and rapidly gather, generate, and evaluate high-quality evidence to guide clinical practice. This is clearly apparent in the accelerated process of assessing and formulating clinical practice guidelines so they can be meaningful during the compressed time frame of a pandemic. A good example of the natural tension that exists between methodologic purity and the clinical relevance of COVID-19–associated guidelines lies with the 2021 American Society of Hematology (ASH) Guidelines on the use of anticoagulation in patients with COVID-19 who are being discharged from the hospital (Table 1).[1]

The guideline authors issued a conditional recommendation against the use of outpatient anticoagulant prophylaxis for patients with COVID-19 who are being discharged from the hospital.[1] However, as the authors themselves suggest, the overall low quality of evidence on the topic of post-discharge thromboprophylaxis for hospitalized patients with COVID-19 requires careful interpretation of and judgment regarding direct evidence in this population and indirect evidence from hospitalized medically ill populations without COVID-19. It is here that the authors' interpretations are subject to some bias or are not entirely based on a holistic or complete interpretation of the available clinical data. Importantly, 3 main issues stand out: (1) definition of the relevant population of hospitalized patients with COVID-19 who are at high risk of thrombosis after discharge, (2) choice of relevant outcomes, including balancing desirable vs undesirable effects of a thromboprophylactic strategy, and (3) methods of incorporating high-quality evidence in a timely fashion.

With regard to the first issue, defining which hospitalized patients with COVID-19 would benefit from a post-discharge thromboprophylactic strategy is critical for assessing the potential benefits of such a strategy. From a clinical perspective, the authors' recommendation against using anticoagulant thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital should reflect the fact that routine use of such a strategy should be avoided in hospitalized patients who have COVID-19, but this begs the question of which patients at high risk of thrombosis might benefit from this strategy. This was indeed the key issue with similar recommendations from the 2018 ASH Guidelines on post-discharge thromboprophylaxis in medically ill patients who did not have COVID 19. Those guidelines failed to incorporate clinical data that supported medically ill patients who had high risk of thrombosis and low risk of bleeding (including those with pneumonia and sepsis) who clearly benefited from extended post-discharge thromboprophylaxis. This led to the regulatory approval of 2 direct oral anticoagulants, betrixaban and rivaroxaban, for this indication.[2-4]

The authors state that no (thrombotic) risk assessment models (RAMs) have been specifically derived or prospectively validated in patients with COVID-19. In addition, they include the International Medical Prevention Registry on Venous Thromboembolism-DD (IMPROVE-DD) venous thromboembolism (VTE) RAM (which is a refinement of the well-validated IMPROVE VTE RAM that incorporates elevated D-dimers) in an RAM for hospitalized patients who do not have COVID that has been externally validated in patients with COVID-19.[1] However, the authors' views have several flaws. The original weighted and

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**Table 1. Summary of the July 2021 Update of the ASH Living Guidelines on the use of anticoagulation for post-discharge thromboprophylaxis**

**Recommendation:** The ASH guideline panel *suggests against* using outpatient anticoagulant thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and who have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects)

**Remarks:** An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision-making are important when deciding whether to use post-discharge thromboprophylaxis. Prospectively validated risk assessment models to estimate the risk of thrombosis and bleeding in patients with COVID-19 after they have been discharged from the hospital are not available. The panel acknowledged that post-discharge thromboprophylaxis may be reasonable in patients judged to be at high risk of thrombosis and low risk of bleeding.

The panel judged the benefits and hazards of post-discharge thromboprophylaxis to be trivial in terms of absolute effects. Even though there was a trivial mortality benefit (5 fewer deaths [from 7 fewer to 2 fewer deaths] per 1000 patients and reduction in VTE (4 fewer [from 9 fewer to 4 more]) per 1000 patients, this evidence was of very low certainty.[1]

scored IMPROVE-DD VTE RAM was derived in a population of hospitalized medically ill patients who had viral and other pneumonias (of which the COVID-19 population is a subset) and who had a similar median hospital length of stay of 4.5 days.[5,6]

The second issue (delineated in the seminal work by McGinn et al[7]) concerns the use of clinical decision rules and notes that external validation of these rules need not be prospective, but it should include multiple settings that incorporate a broad spectrum of patients; indeed, this can most likely be achieved by using retrospective study designs. The IMPROVE-DD VTE RAM has undergone 2 large external validation studies with nearly 19 000 hospitalized patients with COVID-19 by using the original model cutoff: a score of 4 or more predicted a high risk of VTE among the group of inpatients who had COVID-19. It has also shown reasonable discrimination, with an area under the curve of ~0.70.[8,9] In another external validation study, the RAM was a strong and independent predictor of thrombosis and mortality in those patients classified as high risk of VTE.[10] In the largest prospective post-discharge registry encompassing nearly 5000 hospitalized patients with COVID-19, the IMPROVE-DD VTE model using a cutoff score of 4 was an independent predictor of post-discharge thromboembolic outcomes and mortality (odds ratio, 1.51; 95% confidence interval, 1.06-2.14).[11] Most importantly, the IMPROVE VTE RAM using a cutoff score of 4 or more or a score of 2 or 3 with elevated DD was used prospectively in the seminal extended post-discharge clinical randomized trial of inpatients with COVID-19–the MICHELLE trial–to select an inpatient group with COVID-19 who were at high risk for thromboembolism and cardiovascular mortality.[12,13] It is clear from these data that the IMPROVE VTE RAM or its derivative incorporating elevated DD is not only the most extensively validated thrombotic tool in hospitalized patients with COVID-19, but it can also be used prospectively to identify a group of inpatients with COVID-19 at high risk of thrombosis who benefited from extended post-hospital discharge thromboprophylaxis (Table 2).

With regard to the second issue, we have clear evidence at this point that COVID-19 in hospitalized patients produces a severe

**Table 2. External validation or prognostic use of the IMPROVE-DD VTE score to identify hospitalized patients who have COVID-19 and a high risk of thrombosis in the post-discharge period**

| Study | Year | N | Type | Results | Comments |
|---|---|---|---|---|---|
| Paz Rios et al[10] | 2020 | 184 | Retrospective observational study | Moderate risk for VTE (HR, 5.68; 95% CI, 2.93-11.03; $P < .001$) and high risk for VTE (HR, 6.22; 95% CI, 3.04-12.71; $P < .001$) by IMPROVE VTE score had significant association with mortality, 87% sensitivity, and 63% specificity (AUC, 0.752; $P < .001$). | High risk for VTE by IMPROVE VTE score was associated with thrombotic events (HR, 6.50; 95% CI, 2.72-15.53; $P < .001$). |
| Spyropoulos et al[8] | 2021 | 9407 | Retrospective external validation study | VTE rate was 0.4% for IMPROVE-DD VTE score 0-1 (low risk), 1.3% for score 2-3 (moderate risk), and 5.3% for score ≥4 (high risk). ROC AUC, 0.702. | Of the total population, 45% scored high risk for VTE and 21% scored low risk. IMPROVE-DD discrimination of low risk vs medium risk or high risk showed sensitivity, 0.971; specificity, 0.218; PPV, 0.036; and NPV, 0.996. |
| Goldin et al[9] | 2021 | 9407 | Retrospective external validation study | VTE rate was 0.41% for IMPROVE-DD score 0-1 (low risk), 1.21% for score 2-3 (moderate risk), and 5.30% for score ≥4 (high risk). ROC AUC, 0.703. | In all, 45.7% of patients were classified as high risk of VTE, 33.3% moderate risk, and 21.0% low risk. Discrimination of low vs moderate risk or high risk of VTE demonstrated sensitivity, 0.971; specificity, 0.215; PPV, 0.036; and NPV, 0.996. |
| CORE-19 Registry[11] | 2021 | 4906 | Prospective registry | IMPROVE-DD VTE model using a cutoff score of ≥4 was an independent predictor of post-discharge thromboembolic outcomes and mortality (OR, 1.51; 95% CI, 1.06-2.14). | Post-discharge anticoagulation was significantly associated with reduction in primary outcomes of major thromboembolism and mortality (OR, 0.54; 95% CI, 0.47-0.81). |
| MICHELLE trial[13] | 2021 | 320 | Randomized controlled trial | The primary efficacy outcome occurred in 5 (3%) of 159 patients assigned to rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk, 0.33; 95% CI, 0.12-0.90; $P = .0293$). No major bleeding occurred in either study group. | An IMPROVE VTE score of ≥4 or a score of 2-3 with elevated DD (>2 × ULN) was the key enrichment criterium. |

AUC, area under the curve; CI, confidence interval; DD, D-dimer; HR, hazard ratio; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; ROC, receiver operating characteristic [curve]; ULN, upper limit of normal; VTE, venous thromboembolism.

COVID-19–specific coagulopathy manifested by dysregulated thrombin generation much more than a bleeding diathesis.[14] A review of the evidence tables for the article reveals an overall low certainty in the evidence, which is consistent with data that come mostly from observational studies.[1] However, the evidence tables reveal (in absolute terms) the benefits of 5 fewer deaths and 4 fewer VTE events per 1000 inpatients with COVID-19 who have a post-discharge antithrombotic strategy vs 1 more major bleed per 1000 patients.[1] The panel judged that both benefits and harms of post-discharge thromboprophylaxis were trivial, based on a defined estimated incidence of fewer than 5 events per 1000 patients. However, the clinical severity of efficacy and safety pairings should be taken into account when evaluating an overall antithrombotic strategy during the development of guidelines. Indeed, in previous antithrombotic guidelines, 5 fewer deaths per 1000 patients from an antithrombotic strategy have been judged as nontrivial and clinically meaningful, and they also form the entire basis of why we give in-hospital thromboprophylaxis.[15,16]

The third issue, however, is paramount because current guideline panels must be able to incorporate rapidly evolving high-quality data in the setting of the COVID-19 pandemic. Randomized clinical trials conducted during a pandemic should follow the high-quality standards generally used in clinical research. However, the urgent need for assessing new treatments requires leveraging more efficient and innovative research processes to address new challenges in conducting clinical research. In light of these principles, the MICHELLE trial was conducted in 14 centers in Brazil in ~9 months. It showed that the patients at high risk for thrombotic complications (defined as having an IMPROVE VTE score of 4 or more or a score of 2 or 3 with elevated DD) and low risk of bleeding who received thromboprophylaxis with rivaroxaban 10 mg once per day for 35 days vs no anticoagulation had a 67% relative risk reduction in the primary outcome. The primary outcome was a composite of major thromboembolic events and cardiovascular death.[12] Importantly, no major bleeding events were seen with this strategy.[12] Therefore, these results illustrate that despite having a relatively small sample size, the antithrombotic sweet spot for post-discharge thromboprophylaxis in patients with COVID-19 was found by using the right study design, by carefully selecting the population, and by making an appropriate choice of antithrombotic regimen. Given this contemporary and randomized evidence to guide the care of patients with COVID-19, it is surprising to see that this background work in identifying a population with high risk of thrombosis using a validated VTE RAM and primary results of the MICHELLE trial was not incorporated into the 2021 ASH guidelines for post-discharge extended anticoagulation in patients with COVID-19, especially during a pandemic in which high-quality evidence is desperately needed.

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