Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COMMENTARY

blood advances

TO THE EDITOR:

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

Alex C. Spyropoulos,[1-3] and Renato D. Lopes[4,5]

[1]The Institute for Health System Science, The Feinstein Institutes for Medical Research and The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [2]Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, New York, NY; [3]Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia; [4]Duke Clinical Research Institute, Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, NC; and [5]Brazilian Clinical Research Institute, Sao Paulo, SP, Brazil

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

Submitted 8 February 2022; accepted 24 February 2022; prepublished online on *Blood Advances* First Edition 4 March 2022; final version published online 30 August 2022. DOI 10.1182/bloodadvances.2021006871.

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.

Acknowledgments: The authors thank Ioannis Koulas, MD, for his help in preparing this manuscript.
A portion of this work was funded by the Broxmeyer Fellowship in Clinical Thrombosis.

Contribution: A.C.S. and R.D.L. analyzed data and wrote the article.

Conflict-of-interest disclosure: A.C.S. received research grants and served as a consultant for Janssen Research & Development, Bayer, Portola, Boehringer Ingelheim, Bristol Meyers Squibb, and ATLAS group. R.D.L. has received grants from Bristol Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and Sanofi; consulting fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, Portola, and Sanofi; and honoraria for lectures from Bristol Myers Squibb, Pfizer, and Bayer.

ORCID profile: A.C.S., 0000-0002-3175-461X.

Correspondence: Alex C. Spyropoulos, Feinstein Institutes for Medical Research, Northwell Health at Lenox Hill Hospital, 130 E 77th St, New York, NY 10075; e-mail: aspyropoul@northwell.edu.

References

1. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: July 2021 update on postdischarge thromboprophylaxis. *Blood Adv.* 2022;6(2):664-671.
2. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv.* 2018;2(22):3360-3392.
3. Spyropoulos AC, Lipardi C, Xu JF, et al. Improved benefit risk profile of rivaroxaban in a subpopulation of the MAGELLAN study. *Clin Appl Thromb Hemost.* 2019;25:1076029619886022.
4. Spyropoulos AC, Levy JH, Ageno W, et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost.* 2020;18(8):1859-1865.
5. Gibson CM, Spyropoulos AC, Cohen AT, et al. The IMPROVEDD VTE Risk Score: incorporation of D-dimer into the IMPROVE score to improve venous thromboembolism risk stratification. *TH Open.* 2017;1(1):e56-e65.
6. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA.* 2020;323(20):2052-2059.
7. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS; Evidence-Based Medicine Working Group. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. *JAMA.* 2000;284(1):79-84.
8. Spyropoulos AC, Cohen SL, Gianos E, et al; COVID-19 Consortium Group. Validation of the IMPROVE-DD risk assessment model for venous thromboembolism among hospitalized patients with COVID-19. *Res Pract Thromb Haemost.* 2021;5(2):296-300.
9. Goldin M, Lin SK, Kohn N, et al. External validation of the IMPROVE-DD risk assessment model for venous thromboembolism among inpatients with COVID-19. *J Thromb Thrombolysis.* 2021;52(4):1032-1035.
10. Paz Rios LH, Minga I, Kwak E, et al. Prognostic value of venous thromboembolism risk assessment models in patients with severe COVID-19. *TH Open.* 2021;5(2):e211-e219.
11. Giannis D, Allen SL, Tsang J, et al. Postdischarge thromboembolic outcomes and mortality of hospitalized patients with COVID-19: the CORE-19 registry. *Blood.* 2021;137(20):2838-2847.

12. Ramacciotti E, Agati LB, Calderaro D, et al. Medically ill hospitalized patients for COVID-19 THrombosis Extended ProphyLaxis with rivaroxaban ThErapy: Rationale and Design of the MICHELLE Trial. *Am Heart J.* 2021;242:115-122.

13. Ramacciotti E, Barile Agati L, Calderaro D, et al; MICHELLE investigators. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet.* 2022;399(10319):50-59.

14. Bikdeli B, Madhavan MV, Jimenez D, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75(23):2950-2973.

15. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008; 133(6 suppl):381S-453S.

16. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):e195S-e226S.