

**LETTER TO THE EDITOR**

# Authors' response to "Venous Thromboembolism Risk Models in Hospitalized Medical Patients: The Time for Implementation, Not Never-Ending Development"

**KEYWORDS**

adult, bleeding, inpatients, risk assessment, venous thrombosis

Dear Dr Makris and Editorial Board,

We respect Dr Spyropoulos' and Ramacciotti's opinions on the strengths and weaknesses of our published study [1]. We also stand by our published results and conclusions [2].

There are a few clarifications that we would like to make concerning the comments made. The first concerns the choice of risk assessment model to be validated. We laid out the rationale clearly in our discussion. We chose the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) predictive (4-variable) model, not the IMPROVE associative (7-variable) model, because the risk factors were assessed at admission prior to the occurrence of all venous thromboembolism (VTE) events [3]. We do acknowledge the modified IMPROVE model, which incorporates D-dimer into the 7-variable model. However, D-dimer is assessed in less than 10% of medical admissions at the University of Vermont (UVM) Medical Center and other health systems and would require additional laboratory testing on millions of people annually [4]. For postdischarge VTE prophylaxis, Drs Spyropoulos and Ramacciotti cite the International Angiology guidelines, which were published in February 2024, around the time this manuscript was submitted [5]. The International Angiology guidelines from 2024 suggest that extended duration prophylaxis may be considered on an individual basis, which is similar to the recommendations from the International Angiology 2013 guidelines [6]. When reviewing the same evidence base in 2018 and the updated evidence base in 2023, the American Society of Hematology's consensus statement does not recommend routine postdischarge prophylaxis [7,8]. These statements reflect a difference in wording, not in substance.

The second point is about the methods of the validation of the score. Calibration and clinical utility are a common downfall of risk assessment models and must be differentiated from discrimination [9–12]. Readers can use Table 3 in the manuscript we published in Research and Practice in Thrombosis and Haemostasis to assess both the calibration and the clinical utility of various 4-variable IMPROVE cutoff definitions [2]. If we used the trinary cutoff proposed for

IMPROVE by Drs Spyropoulos and Ramacciotti, 88% of the population and 67% of the VTE cases would be low risk in their original study [3]. This is modestly better in the UVM population, with 71% of the population and 49% of VTE cases being low risk. High risk would include 2% of the population from the original IMPROVE study and 6% of the UVM cohort, with 15% and 21% of the VTE cases being high risk, respectively [2]. Other authors have externally validated the 7-variable IMPROVE model, and we would refer readers to this published paper and an accompanying editorial comment [13,14].

In conclusion, we must always ask if the tools we use in medical care are those that are best fit for the purpose we employ them. Medical care changes over time, and our tools need retuning. The underlying precepts of medicine are more durable—to improve the lives of those we care for and minimize harm. In this, we and Drs Spyropoulos and Ramacciotti agree. Risk of VTE should be assessed for medical patients, and preventive measures should be employed for those in whom the benefits outweigh the risks.

Sincerely

Neil A. Zakai, MD, MSc, on behalf of our authorship team

**AUTHOR CONTRIBUTIONS**

N.A.Z. drafted and revised the manuscript. All authors provided critical scientific input and revised the manuscript.

**RELATIONSHIP DISCLOSURE**

The authors report no relevant conflicts of interest.

**FUNDING INFORMATION**

This study was funded by grant R01-HL141290 (N.A.Z.) from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, United States of America. The sponsoring institution was not involved in the analytic approach or data review. The views presented here represent those of the authors and not necessarily of the National Institutes of Health. H.A.-S. is funded by the National Heart, Lung, and Blood Institute (1K23HL159313). We appreciate the support and guidance of investigators from the Study Design and Molecular Epidemiology Core of the Vermont Center for Cardiovascular and Brain Health. Funding was provided by P20

GM135007 from the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health.

Neil A. Zakai<sup>1,2,3</sup>   
 Katherine S. Wilkinson<sup>2</sup>  
 Andrew D. Sparks<sup>4</sup>  
 Mansour Gergi<sup>1,3</sup>  
 Allen B. Repp<sup>1,3</sup>  
 Hanny Al-Samkari<sup>5</sup>  
 Ryan Thomas<sup>1,3</sup>  
 Nicholas S. Roetker<sup>6</sup>

<sup>1</sup>Department of Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

<sup>2</sup>Department of Pathology and Laboratory Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

<sup>3</sup>University of Vermont Medical Center, Burlington, Vermont, USA

<sup>4</sup>Department of Medical Biostatistics, Biomedical Statistics Research Core, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

<sup>5</sup>Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

<sup>6</sup>Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, Minnesota, USA

Handling Editor: Michael Makris

#### Correspondence

Neil A. Zakai, University of Vermont College of Medicine, 360 South Park Drive, Colchester, VT 05446, USA.  
 Email: [neil.zakai@med.uvm.edu](mailto:neil.zakai@med.uvm.edu)

#### ORCID

Neil A. Zakai  <https://orcid.org/0000-0001-8824-4410>

#### REFERENCES

- [1] Spyropoulos AC, Ramacciotti E. Venous thromboembolism risk models in hospitalized medical patients: the time for implementation, not never-ending development. in press. *Res Pract Thromb Haemost.* 2024. <https://doi.org/10.1016/j.rpth.2024.102473>.
- [2] Wilkinson KS, Sparks AD, Gergi M, Repp AB, Al-Samkari H, Thomas R, et al. Validation of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk scores for venous thromboembolism and bleeding in an independent population. *Res Pract Thromb Haemost.* 2024;8:102441. <https://doi.org/10.1016/j.rpth.2024.102441>
- [3] Spyropoulos AC, Anderson FA Jr, FitzGerald G, Decousus H, Pini M, Chong BH, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest.* 2011;140:706–14.
- [4] Zakai NA, Wilkinson K, Sparks AD, Packer RT, Koh I, Roetker NS, et al. Development and validation of a risk model for hospital-acquired venous thrombosis: the Medical Inpatients Thrombosis and Hemostasis study. *J Thromb Haemost.* 2024;22:503–15.
- [5] Nicolaides AN, Fareed J, Spyropoulos AC, Kakkar RHL, Antignani PL, Avgerinos E, et al. Prevention and management of venous thromboembolism. International Consensus Statement. Guidelines according to scientific evidence. *Int Angiol.* 2024;43:1–222.
- [6] Nicolaides A, Fareed J, Kakkar AK, Comerota AJ, Goldhaber SZ, Hull R, et al. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). *Clin Appl Thromb Hemost.* 2013;19:116–8.
- [7] Rezende SM, Bauer KA, Zakai NA. Thromboprophylaxis in hospitalized and nonhospitalized medical patients: what's new? *Blood Adv.* 2023;7:5199–201.
- [8] Schunemann 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.
- [9] Huang Y, Li W, Macheret F, Gabriel RA, Ohno-Machado L. A tutorial on calibration measurements and calibration models for clinical prediction models. *J Am Med Inform Assoc.* 2020;27:621–33.
- [10] Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW. Topic Group 'Evaluating diagnostic tests and prediction models' of the STRATOS initiative. Calibration: the Achilles heel of predictive analytics. *BMC Med.* 2019;17:230. <https://doi.org/10.1186/s12916-019-1466-7>
- [11] Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. *Heart.* 2012;98:683–90.
- [12] Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart.* 2012;98:691–8.
- [13] Roberts LN, Arya R. Venous thromboembolism risk assessment models for acutely ill medical patients—back to the drawing board? *JAMA Netw Open.* 2024;7:e249952. <https://doi.org/10.1001/jamanetworkopen.2024.9952>
- [14] Häfliger E, Kopp B, Darbellay Farhoumand P, Choffat D, Rossel JB, Reny JL, et al. Risk assessment models for venous thromboembolism in medical inpatients. *JAMA Netw Open.* 2024;7:e249980. <https://doi.org/10.1001/jamanetworkopen.2024.9980>