ORIGINAL ARTICLE

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

Gabor Forgo1 | Evy Micieli1 | Walter Ageno2 | Lana A. Castellucci3 | Gabriela Cesarma-Maus4 | Henry Ddungu5 | Erich Vinicius De Paula6 | Mert Dumantepe7 | Maria Cecilia Guillermo Esposito8 | Stavros V. Konstantinides9 | Nils Kucher1 | Claire McLintock10 | Fionnuala Ní Áinle11,12 | Alex C. Spyropoulos13,14 | Tetsumei Urano15 | Beverley J. Hunt16 | Stefano Barco1,9

1Department of Angiology, University Hospital Zurich, Zurich, Switzerland
2Department of Clinical Medicine, University of Insubria, Varese, Italy
3Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada
4Department of Hematology, Instituto Nacional de Cancerología, Mexico City, Mexico
5Uganda Cancer Institute, Kampala, Uganda
6School of Medical Sciences and Division of Hematology, University of Campinas, Campinas, Brazil
7Department of Cardiovascular Surgery, Uskudar University School of Medicine, Istanbul, Turkey
8Department of Hematology, Hospital de Clinicas Facultad de Medicina, Universidad de la Republica Montevideo, Montevideo, Uruguay
9Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany
10National Women’s Health Auckland City Hospital Auckland New Zealand, Auckland, New Zealand
11Department of Haematology, Mater Misericordiae University Hospital and Rotunda Hospital, Dublin, Ireland
12School of Medicine, University College Dublin, Dublin, Ireland
13Institute for Health Innovations and Outcomes Research, Feinstein Institutes for Medical Research and the Zucker School of Medicine at Hofstra/Northwell, New York, New York, USA
14Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, New York, New York, USA
15Shizuoka Graduate University of Public Health, Shizuoka, Japan
16Thrombosis & Haemophilia Centre, Guys & St Thomas’ NHS Foundation Trust, London, UK

Correspondence
Stefano Barco, Department of Angiology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.
Email: stefano.barco@usz.ch

Abstract

Introduction: Venous thromboembolism (VTE) is a leading cause of cardiovascular morbidity and mortality. The majority of VTE events are hospital-associated. In 2008, the Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) multinational
INTRODUCTION

Venous thromboembolism (VTE) is a leading cause of cardiovascular morbidity and mortality. VTE impairs patient prognosis and causes patient discomfort, longer hospitalizations, and higher health care costs. The majority of VTE events are hospital-associated, occurring during hospitalization or within 90 days of hospital discharge; with more than 20 million hospital admissions in the European Union and around 35 million in the United States per year, there is an urgent need to tackle this issue on a global scale. Several risk assessment models, scores, and classifiers have been developed to identify high-risk medical patients who would benefit from in-hospital and postdischarge thromboprophylaxis on the basis of a risk-benefit principle. This means avoiding exposing patients with a low risk to unnecessary anticoagulation and consequent bleeding risk, but, and conversely, promoting the use of thromboprophylaxis among patients estimated to have a substantial VTE risk.

In several countries, national health care strategies and a systematic approach to prevention of hospital-associated VTE have been integrated into routine care, resulting in a reduction of deaths and costs. However, systematic strategies for VTE prevention are often not uniformly implemented, even within individual countries. The World Health Organization, in cooperation with the World Thrombosis Day and numerous other stakeholders, is currently enacting initiatives to reduce hospital-associated VTE as a part of a global program to reduce preventable mortality from noncommunicable diseases. A key aspect of this process is the evaluation and implementation of currently available assessment measures and therapies.

In 2008, the Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute cross-sectional study reported that only approximately 40% of medical patients at risk of VTE received adequate thromboprophylaxis.

Methods: In our systematic review and meta-analysis, we aimed at providing updated figures concerning the use of thromboprophylaxis globally. We focused on: (a) the frequency of patients with an indication to thromboprophylaxis according with individual models; (b) the use of adequate thromboprophylaxis; and (c) reported contraindications to thromboprophylaxis. Observational nonrandomized studies or surveys focusing on medically ill patients were considered eligible.

Results: After screening, we included 27 studies from 20 countries for a total of 137,288 patients. Overall, 50.5% (95% confidence interval [CI]: 41.9–59.1, $I^2$ 99%) of patients had an indication to thromboprophylaxis: of these, 54.5% (95% CI: 46.2–62.6, $I^2$ 99%) received adequate thromboprophylaxis. The use of adequate thromboprophylaxis was 66.8% in Europe (95% CI: 50.7–81.1, $I^2$ 98%), 44.9% in Africa (95% CI: 31.8–58.4, $I^2$ 96%), 37.6% in Asia (95% CI: 25.7–50.3, $I^2$ 97%), 58.3% in South America (95% CI: 31.1–83.1, $I^2$ 99%), and 68.6% in North America (95% CI: 64.9–72.6, $I^2$ 96%). No major differences in adequate thromboprophylaxis use were found across risk assessment models. Bleeding, thrombocytopenia, and renal/hepatic failure were the most frequently reported contraindications to thromboprophylaxis.

Conclusions: The use of anticoagulants for VTE prevention has been proven effective and safe, but thromboprophylaxis prescriptions are still unsatisfactory among hospitalized medically ill patients around the globe with marked geographical differences.

KEYWORDS

epidemiology, thromboprophylaxis, thrombosis, venous thromboembolism, World Thrombosis Day
Hospital Care Setting (ENDORSE) cross-sectional study with around 70,000 patients from 32 countries showed that there is a substantial proportion of high-risk hospitalized patients, but a low prevalent use of appropriate thromboprophylaxis.\(^1\) In this systematic review of the literature and meta-analysis, we examined the evolution of these figures among acutely ill medical patients in more recent years.

## METHODS

We conducted a systematic review of the literature focusing on the use of risk assessment models and pharmacological thromboprophylaxis in acutely medically ill patients during hospitalization. We screened relevant publications including trials, cohort studies, case-control studies, and surveys in PubMed and Web of Science that appeared over the past decade (2010–) using predefined search terms. Search criteria included “thromboprophylaxis,” “prophylaxis,” and “venous thromboembolism,” also “RAM” and “risk assessment method”; a complete overview of the search criteria has been attached (Appendix S1). Papers were not limited to the English language. The first literature search was on the January 15, 2021, and was updated thereafter. Studies retrieved by a predefined literature search strategy were selected based on titles and abstracts. All parts of the systematic review were performed separately in a standardized manner by two reviewers (G.F. and E.M.).

Studies were considered eligible if they fulfilled the following criteria: (a) observational nonrandomized studies or surveys focusing on medically ill patients (e.g., those who were hospitalized because of a medical, not surgical, condition); and (b) reporting the prevalent use of risk assessment models (and presenting the number of patients for each risk class) and of thromboprophylaxis. A description of each model is presented in the Supplementary Material. In-hospital thromboprophylaxis was defined as the use of pharmacological agents at a prophylactic dose and having been defined as “adequate” in the individual studies based on currently accepted definitions.

We focused on the following study outcomes: (a) patients with an indication for thromboprophylaxis according with individual risk assessment models or classifiers; (b) use of thromboprophylaxis; and (c) reported reasons for not giving thromboprophylaxis to patients with another indication.

The data were extracted using a charting table, which was developed to record key information from sources relevant to the review questions. The findings were descriptively presented, with tables and figures to support the data, when appropriate. The following data were extracted: first author, year of publication, study design, number of study participants, sex, characteristics of the study population, and rate of the outcomes. Search results were screened independently by two reviewers for the relevance of titles/abstracts and full texts of the studies fulfilling the inclusion criteria. Disagreements were solved by a third reviewer.

We performed subgroup analyses investigating separately the frequency of patients classified at high risk and the rate of thromboprophylaxis used in each cohort by focusing on individual models, provided that the number of observations was deemed adequate for a subgroup analysis. We also analyzed the use of adequate thromboprophylaxis among high-risk patients by geographical differences. We calculated weighted and unweighted rates of the outcomes of interest applying a random-effect model (95% confidence interval [CI]). We assessed (statistical) heterogeneity of exposure effects by calculating the \(I^2\) statistic, which summarizes the amount of variance among studies beyond chance. Heterogeneity was defined as low (\(I^2 < 25\%\)), moderate (\(I^2 = 25\%– 75\%\)), or high (\(I^2 > 75\%\)). The presence of publication bias was evaluated by visually inspecting funnel plots. We did not perform a formal quality assessment of the included studies (i.e., with the Newcastle-Ottawa score) because we anticipated that the vast majority of the studies would have not had our research question as one of the predefined outcomes of interest: as a consequence, many items of available scales would have not applied. We have provided a summary of the study design for each study.

## RESULTS

Our literature search identified 2191 records in PubMed and 675 in Web of Science. The process of study selection is summarized in Figure S1. Eventually, we included 27 studies in our analysis for a total of 137,288 patients: of those, 15 were multicentric and six were conducted prospectively. Size, setting, quality assessment, and general characteristics of the included studies are summarized in Table 1. Reflecting their reported use in the studies selected by our systematic review, the following risk assessment models or classifiers were included for analysis: Padua Prediction score, Geneva score, Caprini score, and the American College of Chest Physicians (ACCP) criteria. The baseline characteristics of patients included in the individual studies are summarized in Table 2, including the prevalence of VTE risk factors that would mandate a primary thromboprophylaxis, such as reduced mobility, cancer, cardiopulmonary diseases, prior VTE, and acute infection. The Padua Prediction score \((n = 10, 35\% ; n = 71,649)\) and the scheme proposed by the ACCP guidelines for VTE prophylaxis \((n = 10, 35\% ; n = 4914)\) were the most frequently used models in the literature. Other risk assessment tools included the Caprini \((n = 7, 25\% ; n = 61,258)\) and the Geneva \((n = 1, 3.5\% ; n = 1478)\) scores (Table 3). None of the eligible studies focused on the IMPROVE risk assessment model.

Overall, 50.5\% (95\% CI: 41.9–59.1, \(I^2 99\%\)) of hospitalized medically ill patients were classified as having a high VTE risk according to a risk assessment tool or to the ACCP criteria (Figure 1). This percentage was 30.4\% (95\% CI: 27.4–33.5, \(I^2 97\%\)) for the Padua Prediction score, 59.5\% (95\% CI: 34.9–81.8, \(I^2 99\%\)) for the Caprini score, and 63.1\% (95\% CI: 52.3–73.4, \(I^2 98\%\)) for the ACCP criteria.

Overall, 54.5\% (95\% CI: 46.2–62.6, \(I^2 99\%\)) of patients who were classified to be at a high VTE risk received adequate thromboprophylaxis, defined as the use of pharmacological agents at a prophylactic dose, and had been determined in the individual studies based
| First author       | Centers, n | Study Design | Age (Median) | Men (%) | Country/Region | Exclusion Criteria                                                                 | Number of Patients |
|-------------------|------------|--------------|--------------|---------|----------------|------------------------------------------------------------------------------------|-------------------|
| Grant, 2018       | 52         | n.s.         | 65           | 45      | United States  | <48 h hospitalization, ICU                                                          | 44 775            |
| Flanders, 2014    | 35         | Retrospective| 66           | 43      | United States  | <18 years, pregnancy, surgery during hospitalization, ICU, palliative care, VTE <6 months | 31 260            |
| de Bastos, 2013    | 1          | Cohort       | 65           | 43      | Brazil         | <18 years, ongoing anticoagulation, DVT                                            | 27 221 (surgical and OB/GYN patients included) |
| Gafter-Gvili, 2020| 1          | Retrospective| 67           | 51      | Israel         | <48 h hospitalization, ongoing anticoagulation, surgery, active bleeding, hemoglobin <8 g/dl, platelet count <50 000/ml | 18 890            |
| Mahlab-Guri, 2020 | 1          | Retrospective| 68           | 47      | Israel         | ≤18 years, ongoing anticoagulation, VTE                                           | 3000              |
| Łukaszuk, 2016    | 1          | Retrospective| 66           | 56      | Poland         | <18 years, <24 h hospitalization, ICU                                              | 2011              |
| Nieto, 2014       | 78         | Retrospective| 78           | 51      | Spain          | <40 years, <96 h hospitalization, admission for diagnostic procedures, VTE, surgery | 1623              |
| Spirk, 2015       | 8          | Prospective  | 65           | 53      | Switzerland    | <18 years, ongoing anticoagulation, unable to provide an informed consent          | 1478              |
| Rossetto, 2013    | 1          | n.s.         | 82           | 61      | Italy          | Ongoing anticoagulation, contraindication to anticoagulation                       | 803               |
| Zwicker, 2014     | 5          | Prospective  | 56           | 56      | United States  | Ongoing anticoagulation                                                            | 775               |
| Vazquez, 2014     | 28         | Cross-sectional| 65          | 53      | Argentina      | <21 years, ongoing anticoagulation, pregnancy, postpartum, DVT, ICU                | 729               |
| Kingue, 2014      | 14         | Cross-sectional| 61          | 49      | Sub-Saharan Africa | <40 years                                                                    | 567               |
| Vincentelli, 2016 | 23         | Cohort       | 72           | n.a.    | Italy          | ≤18 years, insufficient medical data, VTE, the presence of caval filters, contraindications for pharmacological prophylaxis, and recent (≤60 days) major trauma or major surgery | 520               |
| Sharif-Kashani, 2012 | 1     | Prospective  | 52           | 62      | Iran           | <18 years, <72 h hospitalization, ongoing anticoagulation, ICU                    | 481               |
| Tazi-Mezalek, 2018 | 7  | Cross-sectional| 60           | n.a.    | Morocco        | <40 years, pregnancy, postpartum, VTE                                              | 467               |
| Farhat, 2018      | 1          | Cross-sectional| n.a.       | n.a.    | Brazil         | <18 years, <24 h hospitalization, ongoing anticoagulation, pregnancy, postpartum, unavailable information | 369               |
| Moorehead, 2017   | 1          | Retrospective| 54           | n.a.    | United States  | INR >1.3, <72 h hospitalization, ongoing anticoagulation, VTE, active bleeding, liver transplantation, active renal or hematologic malignancy, coagulation deficiency | 300               |
| Bâ, 2011         | 12         | Cross-sectional| 62           | 54      | Senegal        | <40 years, VTE                                                                    | 278               |
| First author | Centers, n | Study Design | Age (Median) | Men (%) | Country/Region | Exclusion Criteria | Number of Patients |
|--------------|------------|--------------|--------------|---------|----------------|-------------------|------------------|
| Panju, 2011   | 43         | Retrospective | 23           | n.a.    | Canada         | <18 years, ongoing anticoagulation, no acute illness | 222 |
| Guermaz, 2015 | 44         | Cross-sectional | 40–45       | 52      | Algeria        | <18 years, ongoing anticoagulation, ongoing antithrombotic treatment, no written informed consent | 219 |
| Gharaibeh, 2015 | 45       | Prospective   | 53           | 56      | Jordan         | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 220 |
| Wessels, 2012 | 46         | Cross-sectional | 71           | 46      | South Africa   | <18 years, ongoing anticoagulation, ongoing antithrombotic treatment, no written informed consent | 206 |
| Lanthier, 2010 | 47         | Cross-sectional | 65           | 59      | Cyprus         | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 183 |
| Shah, 2020    | 48         | Cross-sectional | 54           | 48      | Cameroon       | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 124 |
| Nkoke, 2020   | 49         | Cross-sectional | 56           | 48      | Iran           | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 124 |

Abbreviations: DVT, deep vein thrombosis; ICU, intensive care unit; INR, international normalized ratio; n.a., not available or not applicable; OB/GYN, obstetrics and gynecology; SVT, superficial vein thrombosis; VTE, venous thromboembolism.

The results of this systematic review and meta-analysis of global studies indicate that, in contrast to guideline recommendations, the frequency of thromboprophylaxis prescriptions is still unsatisfactory among hospitalized medically ill patients. In 2008, a global multinational cross-sectional survey, the ENDORSE study, including close to 70 000 hospitalized patients from 32 countries, of whom approximately 38 000 were categorized as medical inpatients, showed that 42% of medical inpatients were classified at high risk of VTE defined by the ACCP criteria and only 40% of this subgroup received adequate thromboprophylaxis.13 Our systematic review and meta-analysis of studies published since then, which included more than 135 000 patients from 20 countries, showed that the percentage of adequately thromboprophylaxed patients lags far behind what one would expect, being currently around 54% of those with an indication and after the exclusion of a variable number of patients on therapeutic anticoagulation before hospital admission.

This apparent overall increase of in-hospital thromboprophylaxis over the past decade should be principally read as positive and could have resulted from a number of different reasons, including a general increased awareness of the need for VTE prevention. In comparison with the ENDORSE study, a fair improvement in the rate of the use of adequate thromboprophylaxis is recognizable primarily in Africa among all continents, improving from

on currently accepted definitions. The frequency of thromboprophylaxis use was similar across groups: 56.9% (95% CI: 39.6–73.4, \( I^2 = 99\% \)) for the Padua Prediction score (Figure 2), 53.8% (95% CI: 40.1–67.2, \( I^2 = 98\% \)) for the ACCP criteria (Figure 3), and 50.5% (95% CI: 29.4–71.5, \( I^2 = 99\% \)) for the Caprini score (Figure 4).

The use of adequate thromboprophylaxis was 66.8% in Europe (95% CI: 50.7–81.1, \( I^2 = 98\% \)), 44.9% in Africa (95% CI: 31.8–58.4, \( I^2 = 96\% \)), 37.6% in Asia (95% CI: 25.7–50.3, \( I^2 = 97\% \)), and 58.3% in South America (95% CI: 31.1–83.1, \( I^2 = 99\% \)), whereas the percentage was higher in North America with 68.6% (95% CI: 64.9–72.6, \( I^2 = 96\% \)) of patients (Figure 5).

A total of 14 studies reported the frequency of relative and absolute contraindications to thromboprophylaxis among hospitalized medically ill patients. In five studies, this figure was specified for the total of patients with otherwise a formal indication for its use. In nine studies, it was reported for the total of included patients. A summary of the study characteristics and reasons for not giving thromboprophylaxis is shown in Table 4. Active bleeding was considered a contraindication in all reviewed papers. Following active bleeding, the most prevalent contraindication was thrombocytopenia with cutoff levels varying across studies from <50 000 \( x 10^9/L \) \((n = 5)\), 75 000 \( x 10^9/L \) \((n = 1)\), to 100 000 \( x 10^9/L \) \((n = 2)\). In one study no threshold was defined. A bleeding disorder was reported in seven of the 11 papers as a contraindication. In five studies, patients presenting with renal failure did not receive thromboprophylaxis: the exact definition of renal failure was specified only in two studies.

| TABLE 1 (Continued) |

| First author | Centers, n | Study Design | Age (Median) | Men (%) | Country/Region | Exclusion Criteria | Number of Patients |
|--------------|------------|--------------|--------------|---------|----------------|-------------------|------------------|
| Panju, 2011   | 43         | Retrospective | 23           | n.a.    | Canada         | <18 years, ongoing anticoagulation, no acute illness | 222 |
| Guermaz, 2015 | 44         | Cross-sectional | 40–45       | 52      | Algeria        | <18 years, ongoing anticoagulation, ongoing antithrombotic treatment, no written informed consent | 219 |
| Gharaibeh, 2015 | 45       | Prospective   | 53           | 56      | Jordan         | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 220 |
| Wessels, 2012 | 46         | Cross-sectional | 71           | 46      | South Africa   | <18 years, ongoing anticoagulation, ongoing antithrombotic treatment, no written informed consent | 206 |
| Lanthier, 2010 | 47         | Cross-sectional | 65           | 59      | Cyprus         | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 183 |
| Shah, 2020    | 48         | Cross-sectional | 54           | 48      | Cameroon       | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 124 |
| Nkoke, 2020   | 49         | Cross-sectional | 56           | 48      | Iran           | <18 years, ongoing anticoagulation, no acute illness, >24 h hospitalization, ongoing antithrombotic treatment | 124 |

Abbreviations: DVT, deep vein thrombosis; ICU, intensive care unit; INR, international normalized ratio; n.a., not available or not applicable; OB/GYN, obstetrics and gynecology; SVT, superficial vein thrombosis; VTE, venous thromboembolism.

4 | DISCUSSION

The results of this systematic review and meta-analysis of global studies indicate that, in contrast to guideline recommendations, the frequency of thromboprophylaxis prescriptions is still unsatisfactory among hospitalized medically ill patients. In 2008, a global multinational cross-sectional survey, the ENDORSE study, including close to 70 000 hospitalized patients from 32 countries, of whom approximately 38 000 were categorized as medical inpatients, showed that 42% of medical inpatients were classified at high risk of VTE defined by the ACCP criteria and only 40% of this subgroup received adequate thromboprophylaxis.13 Our systematic review and meta-analysis of studies published since then, which included more than 135 000 patients from 20 countries, showed that the percentage of adequately thromboprophylaxed patients lags far behind what one would expect, being currently around 54% of those with an indication and after the exclusion of a variable number of patients on therapeutic anticoagulation before hospital admission.

This apparent overall increase of in-hospital thromboprophylaxis over the past decade should be principally read as positive and could have resulted from a number of different reasons, including a general increased awareness of the need for VTE prevention. In comparison with the ENDORSE study, a fair improvement in the rate of the use of adequate thromboprophylaxis is recognizable primarily in Africa among all continents, improving from
| First Author               | Reduced Mobility, n (%) | Cancer, n (%) | Respiratory or Heart Failure, n (%) | Prior VTE, n (%) | Obesity, n (%) | Recent Stroke or Myocardial Infarction, n (%) | Acute Infection, n (%) |
|----------------------------|-------------------------|---------------|------------------------------------|-----------------|---------------|-----------------------------------------------|------------------------|
| Gafter-Gvili, 2020         | 2381 (12)               | 3460 (18)     | 934 (5)                            | 150 (1)         | 3602 (19)     | n.a.                                          | 2887 (14)              |
| Mahlab-Guri, 2020          | 831 (28)                | 223 (7)       | 562 (19)                           | 56 (2)          | 387 (13)      | 194 (6)                                       | 951 (32)               |
| Nkoke, 2020                | 45 (31)                 | 4 (3)         | 19 (13)                            | 1 (1)           | 12 (8)        | 9 (6)                                         | n.a.                   |
| Shah, 2020                 | 180 (100)               | n.s.          | 8 (4)                              | n.a.            | 38 (21)       | 8 (4)                                         | n.a.                   |
| Ayalew, 2018               | 44 (21)                 | 18 (9)        | 26 (13)                            | 1 (1)           | n.a.          | 22 (11)                                       | 106 (52)               |
| Farhat, 2018               | 214 (58)                | 25 (7)        | 57 (15)                            | 1 (1)           | 38 (10)       | 12 (3)                                        | 87 (24)                |
| Moorehead, 2017            | 45 (15)                 | 89 (29)       | 14 (5)                             | 82 (27)         | 13 (4)        | n.a.                                          | n.a.                   |
| Łukaszuk, 2016             | n.a.                    | 551 (27)      | 42 (2)                             | 13 (1)          | 349 (17)      | n.a.                                          | 780 (39)               |
| Vincentelli, 2016          | 157 (30)                | 40 (8)        | 160 (30)                           | n.a.            | n.a.          | 18 (3)                                        | 46 (9)                 |
| Gharibeh, 2015             | 84 (surgical patients included) | n.s. | n.a. | n.a. | 92 (42) | n.a. | n.a. |
| Guermaz, 2015              | 61 (27)                 | 7 (3)         | 14 (6)                             | 5 (2)           | 40 (18)       | 19 (8)                                        | 64 (28)                |
| Spirk, 2015                | 403/962 (high risk patients) | 351 (36) | 513 (53) | 120 (13) | 180 (19) | 56 (4) | 403 (42) |
| Flanders, 2014             | n.a.                    | 4334 (21)     | n.a.                              | 1139 (5)        | n.a.          | n.a.                                          | n.a.                   |
| Kingue, 2014               | 132 (23)                | 42 (7)        | n.a.                              | n.a.            | 59 (10)       | 145 (26)                                      | 135 (24)               |
| Nieto, 2014                | 853 (53)                | 93 (6)        | 282 (17)                           | n.a.            | n.a.          | 68 (4)                                        | 279 (17)               |
| Vazquez, 2014              | 330 (45)                | 159 (22)      | 85 (12)                            | 21 (3)          | 330 (45)      | n.a.                                          | n.a.                   |
| Zwicker, 2014              | 54 (10)                 | 528 (10)      | 49 (9)                             | 58 (11)         | 128 (24)      | 5 (1)                                         | 165 (31)               |
| de Bastos, 2013            | n.a.                    | 1096 (11)     | n.a.                              | n.a.            | n.a.          | 1099 (11)                                     | n.a.                   |
| Rossetto, 2013             | 266/296 (high risk patients) | 65 (24) | 120 (31) | 23 (9) | n.a. | 7 (3) | 122 (32) |
| Sharif-Kashani, 2012       | 128 (27)                | 70 (15)       | 13 (3)                             | 4 (1)           | n.a.          | n.a.                                          | n.a.                   |
| Lanthier, 2010             | 71 (39)                 | 29 (16)       | n.a.                              | 8 (4)           | 44 (24)       | n.a.                                          | n.a.                   |

Abbreviations: n.a., not available or not applicable; VTE, venous thromboembolism.
approximately 27%–29% in the ENDORSE study to 45% in this analysis. Moreover, we found that the use of adequate thromboprophylaxis still markedly varied across geographic regions, ranging from 38% in Asia to 69% in North America. This may be due to several factors, including national guidelines, VTE awareness,14 health care standards, variable VTE prevalence among regions,2 and reimbursement system.15 In contrast, we could not find major deviations from model to model, indicating that thromboprophylaxis was given to a similar percentage of patients irrespective of the model that had been used.

Our results also showed that the most frequently reported reasons not to give thromboprophylaxis were the presence of active bleeding or a high risk of bleeding, including thrombocytopenia (with several different cutoffs), and renal or liver dysfunction. In many cases, however, the risk factors for bleeding may also represent predisposing factors for VTE, such as thrombocytopenia in cancer patients, recent trauma, or organ failure. This indicates that alternative preventive measures, such as mechanical thromboprophylaxis, the use of which for patients with contraindications to pharmacological thromboprophylaxis was sparsely mentioned, or novel and possibly

### Table 3: List of the risk assessment models and thromboprophylaxis used in each study

| First Author                  | Risk Assessment Method | Cutoff | Number of Patients | TP Indicated Solely Based on Score | TP Indicated Based on Score in Patients Without Contraindications or Exclusion Criteria | TPiven |
|-------------------------------|------------------------|--------|--------------------|------------------------------------|---------------------------------------------------------------------------------------|--------|
| Grant, 2018                  | Padua ≥4               | 44 775 | 12 226             | 10 422                             | 7955                                                                                 |        |
| Flanders, 2014               | Caprini ≥3             | 31 260 | n.a.               | 20 794                             | 14 563                                                                                |        |
| de Bastos, 2013              | Caprini High risk      | 27 221 | (surgical and OB/ GYN patients included) | n.a.                               | 5227                                                                                 | 1420   |
| Gafter-Gvili, 2020           | Padua ≥4               | 18 890 | n.a.               | 4370                               | 1573                                                                                 |        |
| Mahlab-Guri, 2020            | Padua ≥4               | 3000   | 728                | 618                                | 136                                                                                  |        |
| Łukaszuk, 2016               | Caprini ≥5             | 2011   | n.a.               | 888                                | 309                                                                                  |        |
| Nieto, 2014                  | ACCP 2008              | 1623   | 930                | 771                                | 645                                                                                  |        |
| Spirk, 2015                  | Geneva risk score ≥3   | 1478   | 962                | 898                                | 572                                                                                  |        |
| Rossetto, 2013               | Padua ≥4               | 803    | n.a.               | 296                                | 262                                                                                  |        |
| Zwicker, 2014                | Padua ≥4               | 775    | n.a.               | 377                                | 297                                                                                  |        |
| Vazquez, 2014                | ACCP 2008              | 729    | 729                | 620                                | 385                                                                                  |        |
| Kingue S, 2014               | ACCP 2004              | 567    | n.a.               | 353                                | 128                                                                                  |        |
| Vincentelli, 2016            | Padua n.a.             | 520    | n.a.               | 165                                | 100                                                                                  |        |
| Sharif-Kashani, 2012         | ACCP 2008              | 481    | n.a.               | 221                                | 63                                                                                   |        |
| Tazi-Mezailek, 2018          | ACCP 2008              | 467    | 250                | 250                                | 126                                                                                  |        |
| Farhat, 2018                 | Padua ≥4               | 369    | 154                | 140                                | 91                                                                                   |        |
| Moorehead, 2017              | Padua ≥4               | 300    | n.a.               | 95                                 | 66                                                                                   |        |
| Bâ, 2011                    | ACCP 2004              | 278    | 152                | 136                                | 46                                                                                   |        |
| Panju, 2011                  | ACCP                   | 233    | 233                | 170                                | 91                                                                                   |        |
| Guermaz, 2015               | ACCP                   | 229    | 172                | 152                                | 103                                                                                  |        |
| Gharaibeh, 2015             | Caprini ≥3             | 220    | n.a.               | 127                                | 82                                                                                   |        |
| Wessels, 2012               | Caprini ≥3             | 219    | n.a.               | 154                                | 119                                                                                  |        |
| Ayalew, 2018                | Padua ≥4               | 206    | n.a.               | 78                                 | 21                                                                                   |        |
| Lanthier, 2010              | ACCP                   | 183    | n.a.               | 88                                 | 67                                                                                   |        |
| Shah, 2020                  | Caprini ≥5             | 180    | 140                | 140                                | 82                                                                                   |        |
| Nkoke, 2020                 | Caprini High-risk      | 147    | 139                | 118                                | 26                                                                                   |        |
| Manoucheri, 2015            | ACCP                   | 124    | n.a.               | 114                                | 48                                                                                   |        |

Abbreviations: ACCP, American College of Chest Physicians; n.a., not available or not applicable; OB/GYN, obstetrics and gynecology, TP, thromboprophylaxis.
safer pharmacological agents, are urgently needed to reduce the individual risk of VTE but not that of bleeding. The global VTE burden can be substantially reduced with the implementation of validated risk assessment models in clinical practice, with tailoring individual thromboprophylaxis, and with control measures to assess whether thromboprophylaxis is adequately prescribed. The Padua Prediction score and the ACCP guidelines were the most frequently adopted scores in surveys included in our systematic review, followed by the Caprini and Geneva scores. We noted that applying different risk assessment models to a similar cohort of patients resulted in a different proportion of patients being classified as high risk. Indeed, their performance largely varies, as recently demonstrated in an ad hoc analysis, and their adoption should depend not only on general factors (again, their performance), but also on other aspects, including the target population, general acceptance and collection of specific clinical items for their calculation, and on the expected

---

**FIGURE 1** Patients classified at a high risk of VTE according to risk assessment models or ACCP criteria (all studies). ACCP, American College of Chest Physicians; VTE, venous thromboembolism

**FIGURE 2** Adequate thromboprophylaxis use among high-risk patients according with the Padua Prediction score

**FIGURE 3** Adequate thromboprophylaxis use among high-risk patients according with the ACCP criteria. ACCP, American College of Chest Physicians
VTE prevalence in the target population. Indeed, the present study did not aim to study the performance of the different risk assessment methods, but to focus on the implementation on any strategy to risk stratify medical patients and on its consequences. In fact, some of the included models are not adequately validated for medical patients, such as the Caprini score. In contrast, one of the most frequently validated risk assessment models, the IMPROVE, is probably too "young" to have been introduced in clinical practice and subsequently described in surveys or in population studies.

Raising awareness among health care professionals proved to be a successful method for improving the adequacy of venous thromboprophylaxis. The World Thrombosis Day on October 13 is organized on a yearly basis, with events through the year as well, to raise awareness and improve the care of patients with thrombosis.

The present systematic review and meta-analysis has a number of limitations related to the observational nature of the studies reviewed and their own limitations. Based on our search strategy, some important studies possibly were not included because not all relevant papers may have been listed in PubMed or Web of Science. The studies in our systematic review were a combination of prospective, cross-sectional, and retrospective registries. The risk assessment method used for the revaluation of VTE risk was also diverse with the use of three different risk assessment models plus the ACCP criteria. Furthermore, the cutoff for being classified as high risk for VTE was not homogeneously defined in different studies, and the exclusion criteria were also heterogeneously defined. The high clinical and statistical heterogeneity observed across studies, finally, may prevent an obvious interpretation of these results.

In conclusion, hospital-associated VTE is known to be a mostly preventable cause of morbidity and mortality in medical hospitalized patients. The use of anticoagulants for VTE prevention has been proven effective and safe, but thromboprophylaxis prescriptions are still unsatisfactory among hospitalized medically ill patients around the globe with marked geographical differences.

ACKNOWLEDGEMENTS
Open Access Funding provided by Universitat Zurich.

CONFLICTS OF INTEREST
Dr. Barco has received honoraria from Boston Scientific, Concept Medical, INARI, Bayer, LeoPharma; institutional grants from Sanofi, Bard, Bentley, Concept Medical, Boston Scientific, Concept Medical; and support for congress participation and travel from Daiichi Sankyo and Bayer. Dr. Áinle: research grants (paid to university): Bayer, Daiichi-Sankyo, Actelion, Leo Pharma. Dr. Ageno has received research support from Bayer and honoraria from Aspen, Bayer, BMS/Pfizer, Leo Pharma, Norgine, Sanofi, Daiichi Sankyo. Dr. Castellucci has received honoraria from Bayer, BMS-Pfizer Alliance, The Academy, LEO Pharma, Sanofi, and Servier; she holds a Heart and Stroke Foundation of Canada National New Investigator Award, and a Tier 2 research Chair in Thrombosis and Anticoagulation Safety from the University of Ottawa. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS
Gabor Forgo: data collection, data analysis and interpretation, drafting the article. Maria Cecilia Guillermo Esposito: data collection, revision of the article, provided critical feedback and interpretation of the results, final approval. Walter Ageno, Lana A. Castellucci, Gabriela Cesarmanciu-Maus, Henry Ddungu, Erich Vinicius De Paula, Mert Dumantepe, Maria Cecilia Guillermo Esposito, Stavros V. Konstantinides, Nils Kucher, Claire McLintock, Fionnuala Ní Áinle, Alex C. Spyropoulos,
### TABLE 4 Contraindications to pharmacological thromboprophylaxis as listed in each study

| Study            | Contraindicated/Total Patients, n | Bleeding, n(%) | Definition of Bleeding                                      | Thrombocytopenia, n(%) | Definition of Thrombocytopenia (10⁹/l) | Renal Failure, n(%) | Definition of Renal Failure | Other Reasons, n(%) |
|------------------|-----------------------------------|----------------|-------------------------------------------------------------|------------------------|----------------------------------------|---------------------|-----------------------------|------------------------|
| Guermaz, 2015    | 38/229                            | n.a.           | n.s.                                                       | n.s.                   | n.s.                                   | n.s.                | n.s.                        | n.s.                   |
| Panju, 2011      | 63/233                            | n.a.           | Hemoglobin <100 g/L, suspected or active bleeding, recent gastrointestinal bleeding | n.s.                   | <100 000 oder HIT n.s.                 | n.s.                | n.s.                        | n.s.                   |
| Flanders, 2014   | 6398/31 260                       | n.a.           | Gastrointestinal or genitourinary bleeding within the last 6 months; high-bleeding-risk procedure, intracranial hemorrhage within the past year | n.s.                   | <50 000 oder HIT n.s.                  | n.s.                | n.s.                        | Coagulopathy, hypersensitivity to unfractionated or low molecular weight heparin; severe head, spinal cord, or extremity trauma within the 24 h before admission; or intracranial lesion, neoplasm (n.s.) |
| Sharif-Kashani, 2012 | 23/481                          | 6 (27)         | Active gastrointestinal bleeding, massive hemoptysis       | n.s.                   | n.s.                                   | 14 (60%)            | n.s.                        | Hepatic dysfunction, anemia with hematocrit < 30% 17 (73) |
| KIngue, 2014     | 254/567                           | 28 (12)        | Active bleeding, intracranial hemorrhage                   | 21 (8)                 | n.s.                                   | 88 (15.5%)           | n.s.                        | Hepatic dysfunction, known bleeding disorder, aspirin on admission, NSAID on admission, active gastro-duodenal ulcer 205 (80) |
| Ayalew, 2018     | 50/206                            | 15 (30)        | Active bleeding, severe trauma to head or spinal cord with hemorrhage in past 4 weeks | 25 (50)                | <50 000 or coagulopathy                | Hepatic dysfunction 10 (20) |
| Zwicker, 2014    | 247/775                           | 92 (37)        | Active bleeding, history of hemorrhage                     | 163 (66)               | <50 000 or HIT                         | Patient refusal 12 (5) |
| Bà, 2011         | 22/278                            | 8 (36)         | Active bleeding, intracranial hemorrhage                   | n.s.                   | n.s.                                   | Hepatic dysfunction, unknown bleeding syndrome, active duodenal ulcer 14 (64) |
| Study                  | Contraindicated/Total Patients, n | Bleeding, n(%) | Definition of Bleeding                        | Thrombocytopenia, n(%) | Definition of Thrombocytopenia (10⁹/l) | Renal Failure, n(%) | Definition of Renal Failure | Other Reasons, n(%) |
|------------------------|----------------------------------|----------------|----------------------------------------------|------------------------|----------------------------------------|---------------------|---------------------------|----------------------|
| Vazquez, 2014²⁵       | 129/729                          | n.a.           | Active bleeding, recent (in the past 7 days) major bleeding | n.s.                   | <50 000 or coagulopathy                 | n.s.                |                           |                      |
| Mahlab-Guri, 2020²⁹   | 110/728                          | 50 (45)        | Recent bleeding, intracranial hemorrhage in the past year | 39 (35)                | <75 000 or HIT                        | n.s.                |                           | Hepatic dysfunction, active peptic disease, coagulopathy 21 (20) |
| Grant, 2018²⁵         | 1804/12 226                      | n.a.           | Active bleeding, intracranial hemorrhage within the past year; other hemorrhage within the past 6 months | n.s.                   | <50 000 or coagulopathy                | n.s.                |                           | Hemophelia, or other significant bleeding disorder (n.s.) |
| Nieto, 2014³¹         | 159/930                          | n.a.           | Active bleeding, recent intracranial hemorrhage; Active gastrointestinal ulcer | n.s.                   | n.s.                                   | n.s.                |                           | History of intracranial or aortic aneurysm (n.s.) |
| Nkoke, 2020⁵⁰         | 21/139                           | 12 (57)        | Active bleeding, intracranial hemorrhage         | 1 (8)                  | <100 000                               | 7 (5%)              | Creatinine clearance <30 ml/min | Hepatic impairment 1 (0.7%) |
| Farhat, 2018⁴⁰        | 14/154                           | n.a.           | Active bleeding; ongoing anticoagulation; uncontrolled arterial hypertension (n.s.) | n.s.                   | Cutoff not defined                     | -                   |                           |                      |

Abbreviations: CI, contraindicated; HIT, heparin-induced thrombocytopenia; n.a., not available or not applicable; NSAID, nonsteroidal anti-inflammatory drug.
REFERENCES

1. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res. 2016;118(9):1340-1347.
2. Barco S, Valerio L, Gallo A, et al. Global reporting of pulmonary embolism-related deaths in the World Health Organization mortality database: vital registration data from 123 countries. Res Pract Thromb Haemost. 2021;5(5):e12520.
3. Raskob GE, Spyropoulos AC, Cohen AT, et al. Association between asymptomatic proximal deep vein thrombosis and mortality in acutely ill medical patients. J Am Heart Assoc. 2021;10(5):e019459.
4. Barco S, Woersching AL, Spyropoulos AC, Piovella F, Mahan CE. European Union-28: an annualised cost-of-illness model for venous thromboembolism. Thromb Haemost. 2016;115(4):800-808.
5. Pandor A, Tonkins M, Goodacre S, et al. Risk assessment models for venous thromboembolism in hospitalised adults: a systematic review. BMJ Open. 2021;11(7):e045672.
6. MacDougall K, Spyropoulos AC. New paradigms of extended thromboprophylaxis in medically ill patients. J Clin Med. 2020;9(4):1002.
7. Statista. Total number of hospital admissions in the U.S. from 1946 to 2018. https://www.statista.com/statistics/459718/total-hospital-admission-number-in-the-u-s/. Accessed July 2, 2020.
8. Gateway EHI Number of all hospital discharges. 2020; September 6. Available at: https://gateway.euro.who.int/en/indicators/hfa_535-6011-number-of-all-hospital-discharges/
9. Hunt BJ. Preventing hospital associated venous thromboembolism. BMJ. 2019;365:l4239.
10. Darzi AJ, Karam SG, Charide R, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis. Blood. 2020;135(20):1788-1810.
11. Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients. A systematic review. Thromb Haemost. 2017;117(4):801-808.
12. Dugani S, Gaziano TA. 25 by 25: achieving global reduction in cardiovascular mortality. Curr Cardiol Rep. 2016;18(1):10.
13. Cohen AT, Tapson VF, Bergmann J-F, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet. 2008;371(9610):387-394.
14. Wendelboe AM, McCumber M, Hylek EM, Buller H, Weitz JI, Raskob G. Global public awareness of venous thromboembolism. J Thromb Haemost. 2015;13(8):1365-1371.
15. Mahan CE, Barco S, Spyropoulos AC. Cost-of-illness model for venous thromboembolism. Thromb Res. 2016;145:130-132.
16. Mavromanoli AC, Barco S, Konstantinides SV. Antithrombotics and new interventions for venous thromboembolism: exploring possibilities beyond factor IIa and factor Xa inhibition. Res Pract Thromb Haemost. 2021;5(4). https://doi.org/10.1002/rth2.12509
17. Mahan CE, Liu Y, Turpie AG, et al. External validation of a risk assessment model for venous thromboembolism in the hospitalised acutely-ill medical patient (VTE-VALOUR). Thromb Haemost. 2014;112(4):692-699.
18. Rosenberg D, Eichorn A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC. External validation of the risk assessment model of the international medical prevention registry on venous thromboembolism (IMPROVE) for medical patients in a tertiary health system. J Am Heart Assoc. 2014;3(6):e001152.
19. Germini F, Agnelli G, Fedele M, et al. Padua prediction score or clinical judgment for decision making on antithrombotic prophylaxis: a quasi-randomized controlled trial. J Thromb Thrombolysis. 2016;42(3):336-339.
20. Horner D, Goodacre S, Davis S, Burton N, Hunt BJ. Which is the best model to assess risk for venous thromboembolism in hospitalised patients? BMJ. 2021;373:n1106.
21. Spyropoulos AC, Cohen SL, Gianos E, et al. 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.
22. 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.
23. Sharif-Kashani B, Raeissi S, Bikdeli B, et al. Sticker reminders improve thromboprophylaxis appropriateness in hospitalized patients. Thromb Res. 2010;126(3):211-216.
24. Butkевич LE, Stacy ZA, Daly MW, Huey WY, Taylor CT. Impact of a student-supported pharmacy assessment program on venous thromboembolism prophylaxis rates in hospitalized patients. Am J Pharm Educ. 2010;74(6):105.
25. Grant PJ, Conlon A, Chopra V, Flanders SA. Use of venous thromboembolism prophylaxis in hospitalized patients. JAMA Intern Med. 2018;178(8):1122-1124.
26. Flanders SA, Greene MT, Grant P, et al. Hospital performance for pharmacologic venous thromboembolism prophylaxis and rate of venous thromboembolism: a cohort study. JAMA Intern Med. 2014;174(10):1577-1584.
27. de Bastos M, Barreto SM, Caiafa JS, Bogutchi T, Rezende SM. Assessment of characteristics associated with pharmacologic thromboprophylaxis use in hospitalized patients: a cohort study of 10,016 patients. Blood Coagul Fibrinolysis. 2013;24(7):691-697.
28. Gafter-Gvili A, Drozdinsky G, Zusman O, Kushnir S, Leibovici L. Venous thromboembolism prophylaxis in acute medically ill patients: a retrospective cohort study. Am J Med. 2020;133(12):1444-1452.e3.
29. Mahlab-Guri K, Otman MS, Replianski N, Rosenberg-Bezalel S, Rabinovich I, Sthoeger Z. Venous thromboembolism prophylaxis in patients hospitalized in medical wards: a real life experience. Medicine (Baltimore). 2020;99(7):e19127.
30. Lukaszuk RF, Plens K, Undas A. Real-life use of thromboprophylaxis in patients hospitalized for pulmonary disorders: a single-center retrospective study. Adv Clin Exp Med. 2018;27(2):237-243.
31. Nieto JA, Cámera T, Camacho I. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients. A retrospective multicenter study. Eur J Intern Med. 2014;25(8):717-723.
32. Spirk D, Nendaz M, Aujesky D, et al. Predictors of thromboprophylaxis in hospitalised medical patients. Explicit ASessment of
Thromboembolic Risk and Prophylaxis for Medical Patients in Switzerland (ESTIMATE). Thromb Haemost. 2015;113(5):1127-1134.

33. Rossetto V, Barbar S, Vedovetto V, Milan M, Prandoni P. Physicians’ compliance with the Padua prediction score for preventing venous thromboembolism among hospitalized medical patients. J Thromb Haemost. 2013;11(7):1428-1430.

34. Zwicker JI, Rojan A, Campigotto F, et al. Pattern of frequent but nontargeted pharmacologic thromboprophylaxis for hospitalized patients with cancer at academic medical centers: a prospective, cross-sectional, multicenter study. J Clin Oncol. 2014;32(17):1792-1796.

35. Vazquez F, Watman R, Tabares A, et al. Risk of venous thromboembolic disease and adequacy of prophylaxis in hospitalized patients in Argentina: a multicentric cross-sectional study. Thromb J. 2014;12:15.

36. Kingue S, Bakilo L, Ze Minkande J, et al. Epidemiological African day for evaluation of patients at risk of venous thrombosis in acute hospital care settings. Cardiovasc J Afr. 2014;25(4):159-164.

37. Vincentelli GM, Monti M, Pirro MR, et al. Perception of thromboembolism risk: differences between the departments of internal medicine and emergency medicine. Keio J Med. 2016;65(2):39-43.

38. Sharif-Kashani B, Shahabi P, Raeissi S, et al. Assessment of Prophylaxis for Venous Thromboembolism in hospitalized patients: the MASIH study. Clin Appl Thromb Hemost. 2012;18(5):462-468.

39. Tazi Mezalek Z, Nejjari C, Essadouni L, et al. Evaluation and management of thromboprophylaxis in Moroccan hospitals at national level: the Avail-MoNa study. J Thromb Thrombolysis. 2018;46(1):113-119.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Forgo G, Micieli E, Ageno W, 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;20:409–421. doi:10.1111/jth.15607