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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

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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

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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

1 | INTRODUCTION

Venous thromboembolism (VTE) is a leading cause of cardiovascular morbidity and mortality.[1,2] VTE impairs patient prognosis and causes patient discomfort, longer hospitalizations, and higher health care costs.[3–5] The majority of VTE events are hospital-associated, occurring during hospitalization or within 90 days of hospital discharge[6]: with more than 20 million hospital admissions in the European Union and around 35 million in the United States per year,[7,8] there is an urgent need to tackle this issue on a global scale.[5,9]

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.[5] 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.[10,11]

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.[9] 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.[12] 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

Essentials

- In 2008, ENDORSE reported only 40% of medical patients receiving adequate thromboprophylaxis.
- We did a meta-analysis of 27 studies (N = 137 288) to provide updated figures on a global scale.
- Despite improvement, its use is still unsatisfactory (55%) with marked geographical differences.
- The World Thrombosis Day is instrumental to increase VTE awareness and reduce disease burden.

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.[13] 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.

2 | 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 weighed and unweighed 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.

3 | 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

TABLE 1 Size, setting, and general characteristics of the included studies

First author	Centers, *n*	Study Design	Age (Median)	Men (%)	Country/Region	Exclusion Criteria	Number of Patients
Grant, 2018[25]	52	n.s.	65	45	United States	<48 h hospitalization, ICU	44 775
Flanders, 2014[26]	35	Retrospective	66	43	United States	<18 years, pregnancy, surgery during hospitalization, ICU, palliative care, VTE <6 months	31 260
de Bastos, 2013[27]	1	Cohort	65	43	Brazil	<18 years, ongoing anticoagulation, DVT	27 221 (surgical and OB/GYN patients included)
Gafter-Gvili, 2020[28]	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[29]	1	Retrospective	68	47	Israel	≤18 years, ongoing anticoagulation, VTE	3000
Łukaszuk, 2016[30]	1	Retrospective	66	56	Poland	<18 years, <24 h hospitalization, ICU	2011
Nieto, 2014[31]	78	Retrospective	78	51	Spain	<40 years, <96 h hospitalization, admission for diagnostic procedures, VTE, surgery	1623
Spirk, 2015[32]	8	Prospective	65	53	Switzerland	<18 years, ongoing anticoagulation, unable to provide an informed consent	1478
Rossetto, 2013[33]	1	n.s.	82	61	Italy	Ongoing anticoagulation, contraindication to anticoagulation	803
Zwicker, 2014[34]	5	Prospective	56	56	United States	Ongoing anticoagulation	775
Vazquez, 2014[35]	28	Cross-sectional	65	53	Argentina	<21 years, ongoing anticoagulation, pregnancy, postpartum, DVT, ICU	729
Kingue, 2014[36]	14	Cross-sectional	61	49	Sub-Saharan Africa	<40 years	567
Vincentelli, 2016[37]	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[38]	1	Prospective	52	62	Iran	<18 years, <72 h hospitalization, ongoing anticoagulation, ICU	481
Tazi-Mezalek, 2018[39]	7	Cross-sectional	60	n.a.	Morocco	<40 years, pregnancy, postpartum, VTE	467
Farhat, 2018[40]	1	Cross-sectional	n.a.	n.a.	Brazil	<18 years, <24 h hospitalization, ongoing anticoagulation, pregnancy, postpartum, unavailable information	369
Moorehead, 2017[41]	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[42]	12	Cross-sectional	62	54	Senegal	<40 years, VTE	278

TABLE 1 (Continued)

First author	Centers, *n*	Study Design	Age (Median)	Men (%)	Country/Region	Exclusion Criteria	Number of Patients
Panju, 2011[43]	2	Retrospective	n.a.	n.a.	Canada	<18 years, ongoing anticoagulation	233
Guermaz, 2015[44]	>1	Observational	61	n.a.	Algeria	<40 years, no acute illness	229
Gharaibeh, 2015[45]	1	Cross-sectional	n.a.	52	Jordan	<18 years, <24 h hospitalization, ongoing antithrombotic treatment	220
Wessels, 2012[46]	29	Prospective	53	56	South Africa	<18 years, ongoing anticoagulation, no written informed consent	219
Ayalew, 2018[47]	1	Cross-sectional	40–45	48	Ethiopia	Ongoing anticoagulation	206
Lanthier, 2010[48]	1	Cross-sectional	71	46	Canada	<18 years, ongoing anticoagulation	183
Shah, 2020[49]	2	Prospective	65	59	Cyprus	<18 years, SVT, contraindication to anticoagulation, DVT in the prior 3 months	180
Nkoke, 2020[50]	2	Prospective	54	48	Cameroon	<72 h hospitalization, ongoing anticoagulation, VTE	147
Manoucheri, 2015[51]	1	Cross sectional	n.a.	n.a.	Iran	<16 years, <72 h hospitalization, ongoing anticoagulation	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.

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%), in South America 58.3% (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 $<50\,000 \times 10^9$/L ($n = 5$), 75 000 10^9/L ($n = 1$), to 100 000 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.

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

TABLE 2 Baseline characteristics of patients from the included studies

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[28]	2381 (12)	3460 (18)	934 (5)	150 (1)	3602 (19)	n.a.	2887 (14)
Mahlab-Guri, 2020[29]	831 (28)	223 (7)	562 (19)	56 (2)	387 (13)	194 (6)	951 (32)
Nkoke, 2020[50]	45 (31)	4 (3)	19 (13)	1 (1)	12 (8)	9 (6)	n.a.
Shah, 2020[49]	180 (100)	n.s.	8 (4)	n.a.	38 (21)	8 (4)	n.a.
Ayalew, 2018[47]	44 (21)	18 (9)	26 (13)	1 (1)	n.a.	22 (11)	106 (52)
Farhat, 2018[40]	214 (58)	25 (7)	57 (15)	1 (1)	38 (10)	12 (3)	87 (24)
Moorehead, 2017[41]	n.s.	45 (15)	89 (29)	14 (5)	82 (27)	13 (4)	n.a.
Łukaszuk, 2016[30]	n.a.	551 (27)	42 (2)	13 (1)	349 (17)	n.a.	780 (39)
Vincentelli, 2016[37]	157 (30)	40 (8)	160 (30)	n.a.	n.a.	18 (3)	46 (9)
Gharaibeh, 2015[45]	84 (surgical patients included)	n.s.	n.a.	n.a.	92 (42)	n.a.	n.a.
Guermaz, 2015[44]	61 (27)	7 (3)	14 (6)	5 (2)	40 (18)	19 (8)	64 (28)
Spirk, 2015[32]	403/962 (high risk patients) (42)	351 (36)	513 (53)	120 (13)	180 (19)	56 (4)	403 (42)
Flanders, 2014[26]	n.a.	4334 (21)	n.a.	1139 (5)	n.a.	n.a.	n.a.
Kingue, 2014[36]	132 (23)	42 (7)	n.a.	n.a.	59 (10)	145 (26)	135 (24)
Nieto, 2014[31]	853 (53)	93 (6)	282 (17)	n.a.	n.a.	68 (4)	279 (17)
Vazquez, 2014[35]	330 (45)	159 (22)	85 (12)	21 (3)	330 (45)	n.a.	n.a.
Zwicker, 2014[34]	54 (10)	528 (100)	49 (9)	58 (11)	128 (24)	5 (1)	165 (31)
de Bastos, 2013[27]	n.a.	1096 (11)	n.a.	n.a.	n.a.	1099 (11)	n.a.
Rossetto, 2013[33]	266/296 (high risk patients) (85)	65 (24)	120 (31)	23 (9)	n.a.	7 (3)	122 (32)
Sharif-Kashani, 2012[38]	128 (27)	70 (15)	13 (3)	4 (1)	n.a.	n.a.	n.a.
Lanthier, 2010[48]	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.

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	TP iven
Grant, 2018[25]	Padua	≥4	44 775	12 226	10 422	7955
Flanders, 2014[26]	Caprini	≥3	31 260	n.a.	20 794	14 563
de Bastos, 2013[27]	Caprini	High risk	27 221 (surgical and OB/GYN patients included)	n.a.	5227	1420
Gafter-Gvili, 2020[28]	Padua	≥4	18 890	n.a.	4370	1573
Mahlab-Guri, 2020[29]	Padua	≥4	3000	728	618	136
Łukaszuk, 2016[30]	Caprini	≥5	2011	n.a.	888	309
	Padua	≥4	2011	n.a.	428	167
Nieto, 2014[31]	ACCP 2008		1623	930	771	645
Spirk, 2015[32]	Geneva risk score	≥3	1478	962	898	572
Rossetto, 2013[33]	Padua	≥4	803	n.a.	296	262
Zwicker, 2014[34]	Padua	≥4	775	n.a.	377	297
Vazquez, 2014[35]	ACCP 2008		729	729	620	385
Kingue S, 2014[36]	ACCP 2004		567	n.a.	353	128
Vincentelli, 2016[37]	Padua	n.a.	520	n.a.	165	100
Sharif-Kashani, 2012[38]	ACCP 2008		481	n.a.	221	63
Tazi- Mezalek, 2018[39]	ACCP 2008		467	250	250	126
Farhat, 2018[40]	Padua	≥4	369	154	140	91
Moorehead, 2017[41]	Padua	≥4	300	n.a.	95	66
Bâ, 2011[42]	ACCP 2004		278	152	136	46
Panju, 2011[43]	ACCP		233	233	170	91
Guermaz, 2015[44]	ACCP		229	172	152	103
Gharaibeh, 2015[45]	Caprini	≥3	220	n.a.	127	82
Wessels, 2012[46]	Caprini	≥3	219	n.a.	154	119
Ayalew, 2018[47]	Padua	≥4	206	n.a.	78	21
Lanthier, 2010[48]	ACCP		183	n.a.	88	67
Shah, 2020[49]	Caprini	≥ 5	180	140	140	82
Nkoke, 2020[50]	Caprini	High-risk	147	139	118	26
Manoucheri, 2015[51]	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.

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

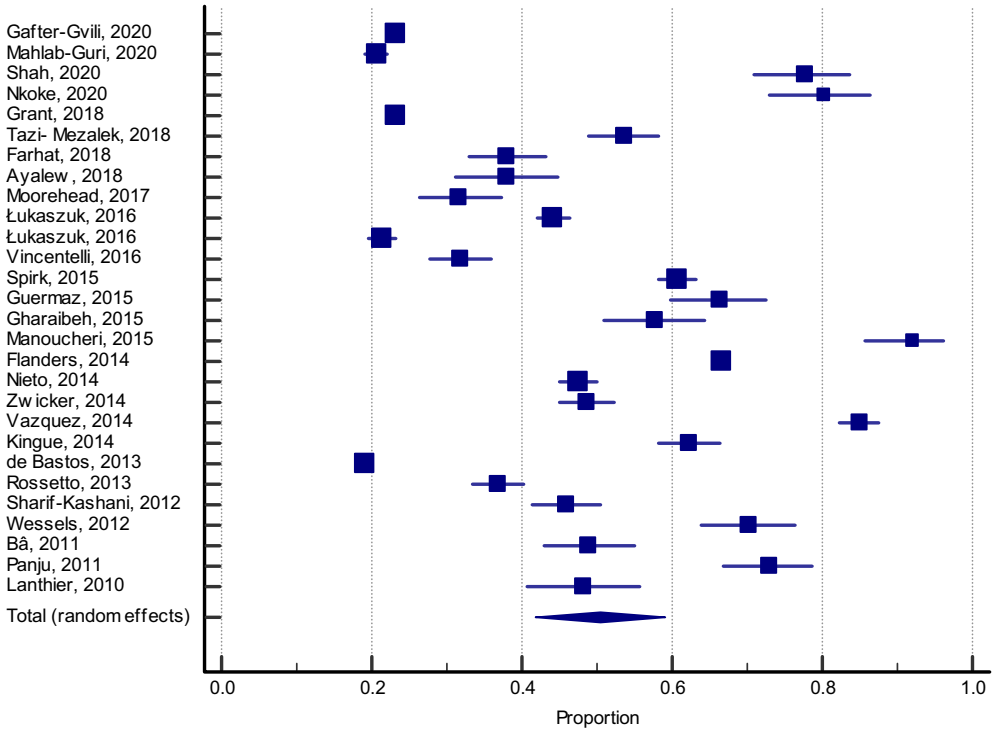

FIGURE 1 Patients classified at a high risk of VTE according to risk assessment models or ACCP criteria (all studies). ACCP, American College of Chest Physicians; VTE, venous thromboembolism

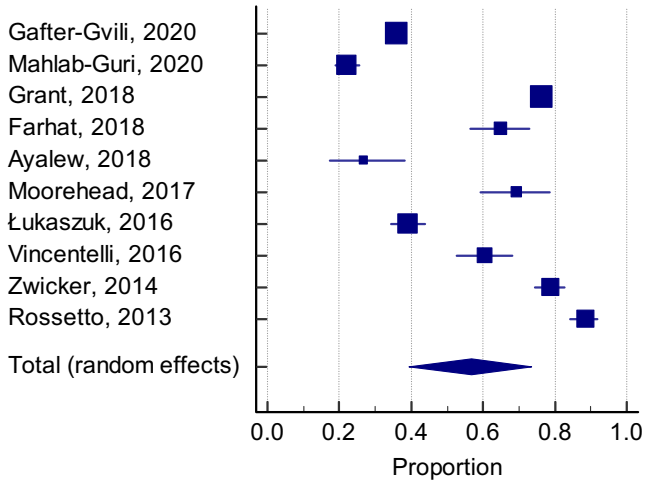

FIGURE 2 Adequate thromboprophylaxis use among high-risk patients according with the Padua Prediction score

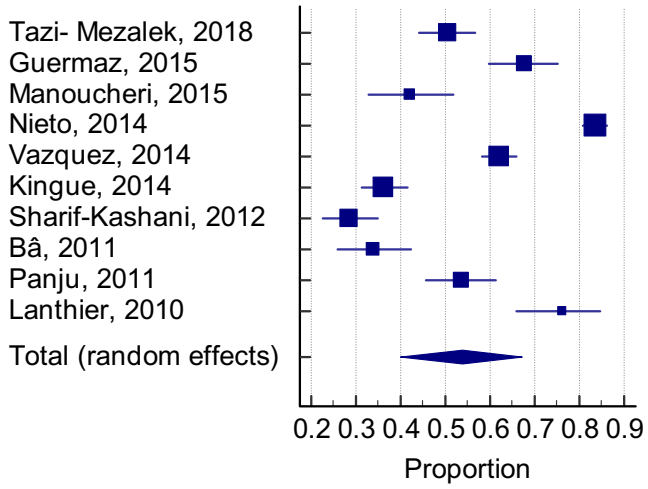

FIGURE 3 Adequate thromboprophylaxis use among high-risk patients according with the ACCP criteria. ACCP, American College of Chest Physicians

safer pharmacological agents,[16] 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.[17–19] 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.[20] Indeed, their performance largely varies, as recently demonstrated in an *ad hoc* analysis,[20] 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

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,[17,21,22] 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.[23,24] 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

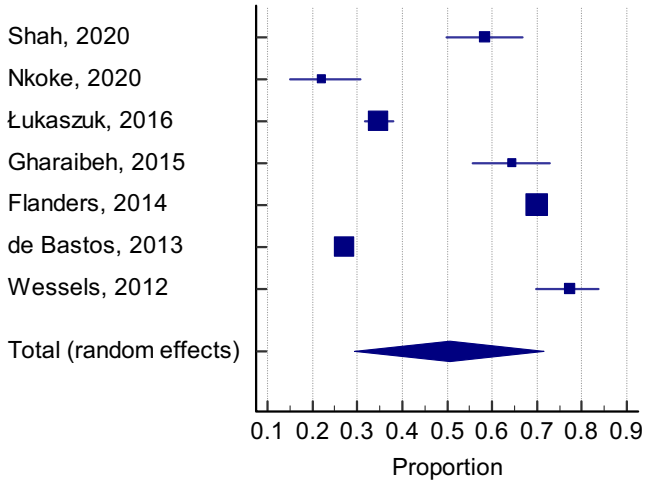

FIGURE 4 Adequate thromboprophylaxis use among high-risk patients according with the Caprini score

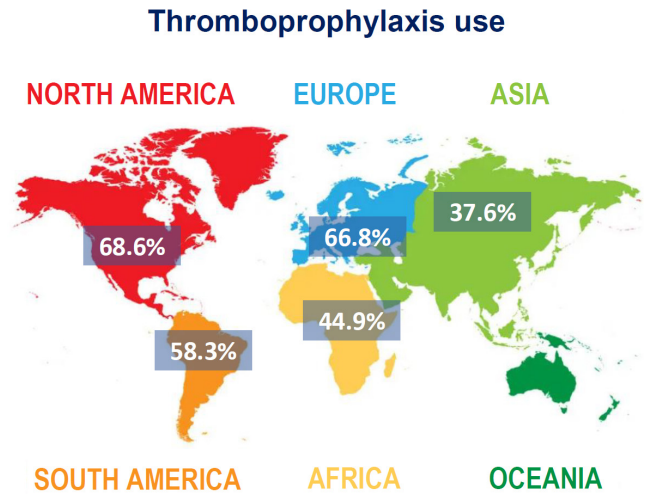

FIGURE 5 Geographical differences in thromboprophylaxis use

with the participation of hundreds of organizations around the globe. It is an educational initiative, with the aim of reducing the disease burden caused by VTE.

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.[52] 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.

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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 Cesarman-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 (10^9/l)	Renal Failure, *n* (%)	Definition of Renal Failure	Other Reasons, *n* (%)
Guermaz, 2015[44]	38/229	n.a.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Panju, 2011[43]	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[26]	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.	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[38]	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[36]	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[47]	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[34]	247/775	92 (37)	Active bleeding, history of hemorrhage	163 (66)	<50 000 or HIT			Patient refusal 12 (5)
Bâ, 2011[42]	22/278	8 (36)	Active bleeding, intracranial hemorrhage	n.s.	n.s.			Hepatic dysfunction, unknown bleeding syndrome, active duodenal ulcer 14 (64)

TABLE 4 (Continued)

Study	Contraindicated/Total Patients, *n*	Bleeding, *n* (%)	Definition of Bleeding	Thrombocytopenia, *n* (%)	Definition of Thrombocytopenia (10^9/l)	Renal Failure, *n* (%)	Definition of Renal Failure	Other Reasons, *n* (%)
Vazquez, 2014[35]	129/729	n.a.	Active bleeding, recent (in the past 7 days) major bleeding	n.s.	<50 000 or coagulopathy	n.s.	Creatinine clearance <30 mL/min	Active peptic ulcer, severe liver failure (n.s.)

Study	Contraindicated/High-risk Patients With Indication, *n*	Bleeding, *n* (%)	Definition of Bleeding	Thrombocytopenia, *n* (%)	Definition of Thrombocytopenia (G/l)	Renal Failure, *n* (%)	Definition of Renal Failure	Other Reasons, *n* (%)
Mahlab-Guri, 2020[29]	110/728	50 (45)	Recent bleeding, Intracranial hemorrhage in the past year	39 (35)	<75 000 or HIT			Hepatic dysfunction, active peptic disease, coagulopathy 21 (20)
Grant, 2018[25]	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			Hemophilia, or other significant bleeding disorder (n.s.)
Nieto, 2014[31]	159/930	n.a.	Active bleeding, recent intracranial hemorrhage; Active gastrointestinal ulcer	n.s.	n.s.			History of intracranial or aortic aneurysm (n.s.)
Nkoke, 2020[50]	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, 2018[40]	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.

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SUPPORTING INFORMATION

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

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