rpth
research & practice
in thrombosis & haemostasis

Unmet definitions in thromboprophylaxis for hospitalized medical patients: An appraisal for the need of recommendation

Bruno Ávila Ferreira BSc[1,2] | Marcos de Bastos MD, PhD[2] | Suely Meireles Rezende MD, PhD[1]

[1]Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[2]Hospital Governador Israel Pinheiro, Belo Horizonte, Brazil

Correspondence
Suely Meireles Rezende, Department of Internal Medicine, Faculty of Medicine Universidade Federal de Minas Gerais, Avenida Alfredo Balena, 190 2nd Floor, Room 255, Belo Horizonte, MG 30130-100, Brazil.
Email: srezende@ufmg.br

Handling Editor: Dr Neil Zakai

Abstract

Up to about 60% of venous thromboembolic events in a community are associated with hospitalization, and most can be prevented by appropriate thromboprophylaxis. Several randomized clinical trials and guidelines have addressed the issue of thromboprophylaxis in hospitalized patients and recommended strategies to assess patients' risk and thromboprophylaxis. Simple and validated risk assessment models are available to assist physicians in selecting patients who are at high risk for VTE, in whom thromboprophylaxis should be used. However, some concepts employed are imprecise or not appropriately defined. Indeed, there has been wide variation in the onset, duration, and adequacy of thromboprophylaxis, as well as in the definition of some risk factors. In this article, we highlight these issues and the unmet definitions in thromboprophylaxis in hospitalized patients mainly by addressing selected randomized clinical trials and guidelines.

KEYWORDS
hospitalization, prophylaxis, thromboprophylaxis, thrombosis, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) mostly manifests as deep vein thrombosis (DVT) and pulmonary embolism. It has an estimated incidence of approximately 1.0–2.7 cases per 1000 person,[1] of which a substantial proportion (up to 60%) are associated with a hospital admission in the previous 90 days.[1,2] Although most VTE events occurring during hospitalization are not associated with symptoms and their clinical impact is probably not substantial, about 65% of the events may be preventable by appropriate thromboprophylaxis.[1,2] Despite this, institution of thromboprophylaxis is still unsatisfactory among hospitalized patients with marked geographic differences.[1,2]

Several randomized clinical trials (RCTs) and guidelines have addressed the issue of thromboprophylaxis in hospitalized patients and recommended strategies to assess patients' risk and thromboprophylaxis.[2–14] Simple and validated risk assessment models (RAMs) are available to assist physicians in selecting patients who are at high risk for VTE. However, some concepts employed are imprecise or not appropriately defined.[2–14] The aim of this article is to highlight these issues as well as the unmet definitions in thromboprophylaxis in hospitalized patients based on selected RCTs and guidelines.

2 | DURATION OF REDUCED MOBILITY AS A RISK FACTOR FOR VTE

The concept of reduced mobility has been vaguely described in studies addressing thromboprophylaxis in hospitalized patients.

Duration of reduced mobility as a risk factor for VTE ranged from 24 h prior to hospital admission to 14 days.[15] The American College of Chest Physicians (ACCP) guideline[4] recommends thromboprophylaxis for those at high risk of VTE while reduced mobility persists or until hospital discharge. However, it does not specify any parameter of reduced mobility, such as its minimum or maximum length.[4] In the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) RAM, decreased mobility is considered when it is present for at least 7 days.[5] In the Padua Prediction Score (PPS),[16] reduced mobility length is considered when it occurs for 3 or more days. The National Institute for Health and Care Excellence (NICE)[6] defines reduced mobility as a risk factor for VTE when there is significant reduction of mobility, that is, when individuals are bedbound, unable to walk without help, or likely to stay a substantial proportion of the day in a chair or in bed.[6] Therefore, reduced mobility has a wide variability of definitions, requiring further refinement and research for standardization as a risk factor for VTE.

3 | ADEQUACY OF THROMBOPROPHYLAXIS

Adequacy of thromboprophylaxis has been poorly addressed across studies.[2] Furthermore, there has been a wide inconsistency of the definition in studies and guidelines.[3–6] The ACCP guideline has proposed three main attributes for appropriate thromboprophylaxis[4]: (i) Patients at increased VTE risk should receive pharmacological thromboprophylaxis at an appropriate dosage; (ii) patients at low risk for VTE should not receive pharmacological thromboprophylaxis; (iii) patients at high risk of VTE and high risk of bleeding should receive mechanical thromboprophylaxis. In addition, the ACCP guideline states that an appropriate thromboprophylaxis shall be prescribed for 6–21 days, until full mobility is restored, or until discharge from hospital, whichever comes first.[4]

Adequacy of thromboprophylaxis has also been proposed by some studies, although with different criteria.[16–19] Some authors[17–19] have followed the definitions of the ACCP guideline, while two of them[17,18] refined the criteria. For those, thromboprophylaxis was considered as adequate if all the following conditions were fulfilled: (i) The prophylactic agent was prescribed as recommended by the ACCP guideline, by using the same type, dose, and frequency of administration; (ii) thromboprophylaxis was regularly prescribed for at least 7 days, until full mobility or hospital discharge, whichever came first; and (iii) prophylaxis was initiated within 24 h of hospital admission.[17,18]

Barbar et al.[16] proposed another definition for adequate thromboprophylaxis, which included implementation within 48 h of hospital admission, daily administration of a minimum dose of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux, which should be used for at least 80% of the hospital stay.

In RCT, adequacy of thromboprophylaxis has not been defined enough for allowing medical care standardization and comparison between studies.[7–14] Furthermore, guidelines lack important attributes for defining adequacy of thromboprophylaxis, such as start and duration of thromboprophylaxis.[3–6] Therefore, well-defined and reproducible criteria are warranted and may improve clinical care and comparability of thromboprophylaxis efficacy between studies.

4 | UNMET DEFINITIONS IN GUIDELINES

To evaluate the recommendation about risk assessment tools for hospitalized patients, we selected four recently published guidelines: (i) American College of Physicians (ACP),[3] (ii) ACCP,[4] (iii) NICE,[6] and (iv) American Society of Hematology (ASH)[5] (Table 1). All four guidelines recommend to ascertain VTE risk in hospitalized patients at hospital admission. The ACP and NICE do not recommend a specific RAM, but both recommend risk assessment for VTE for all patients at hospital admission. NICE[6] adopts two stages of VTE risk assessment: (i) assessment of the level of mobility and (ii) identification of VTE risk factors, including active cancer, age above 60 years, and known thrombophilia, among others.[6] Conversely, the ACCP and ASH guidelines recommend RAMs for individual VTE risk classification but diverge from each other regarding the selection of the tool.[4,5] The ACCP guideline suggests the PPS, and the ASH guideline suggests either PPS or IMPROVE.[4,5] Although both tools (PPS and IMPROVE) have been externally validated and are widely used for VTE risk assessment, their ability to predict VTE risk is considered to be moderate.[2,20]

Despite ACP,[3] ACCP,[4] NICE,[6] and ASH[5] guidelines agree upon the use of pharmacological thromboprophylaxis in patients at risk of VTE, only NICE[6] defines when to start thromboprophylaxis, which is as soon as possible and within 14 h of admission, unless otherwise stated.[6]

Regarding the type of anticoagulant for thromboprophylaxis, all four guidelines agree upon the use of LMWH, UFH (two or three subcutaneous doses per day) or fondaparinux. NICE recommends LMWH as the first option,[6] although there are no data supporting superiority of a specific type of heparin over the other.[6]

In the ACCP guideline, thromboprophylaxis is recommended for a period of 6–21 days, while NICE recommends at least 7 days with no upper limit.[4,6] There is no recommendation for the duration of thromboprophylaxis in the ASH and ACP guidelines.[3,5] All four guidelines recommend against extended thromboprophylaxis beyond hospital discharge for medical patients.[3–6]

5 | UNMET DEFINITIONS AND OUTCOMES ON RANDOMIZED CLINICAL TRIALS ADDRESSING THROMBOPROPHYLAXIS

We evaluated definitions of thromboprophylaxis in eight large RCTs, which included more than 1000 hospitalized medical patients at risk

TABLE 1 Criteria for thromboprophylaxis in hospitalized medical patients according to selected guideline and randomized clinical trials

Guidelines

Guideline	Indication for TP	Start of TP	Duration of TP	Class of anticoagulant/dose	RAM	Reassessment of risk of VTE	Outcome	Extended TP	Reference
ACP	High risk for VTE	N/A	The optimal duration of TP is uncertain	Recommends pharmacologic TP with heparin or a related drug	The current evidence is insufficient to recommend a validated tool	N/A	Mortality up to 120 days	Not recommended	[3]
ACCP	For patients at increased risk for VTE	N/A	6–21 days, until full mobility is restored, or until discharge from hospital, whichever comes first	Recommends TP with LMWH, UFH twice or three times a day, or fondaparinux	Padua Prediction Score	N/A	Symptomatic DVT and PE	Not recommended	[4]
NICE	For patients at increased risk for VTE	As soon as possible after admission to hospital or by the time of the first consultant review	Pharmacological TP for a minimum of 7 days to acutely ill medical patients whose risk of VTE outweighs their risk of bleeding	LMWH as first-line treatment. If LMWH is contraindicated, use fondaparinux sodium	NICE Risk assessment	Reassess for risk of VTE at the point of consultant review or if patients' clinical condition change	DVT and PE	Not recommended	[5]
ASH	N/A	N/A	N/A	Suggests using UFH, LMWH, or fondaparinux	Padua Prediction Score or IMPROVE	N/A	Mortality, PE and moderate to severe DVT	Not recommended	[6]

Randomized clinical trials

RCT	Indication for TP	Start of TP	Duration of TP	Class of anticoagulant/dose	RAM	Reassessment of risk of VTE	Outcome	Extended TP	Reference
MEDENOX	Age ≥40 years; Expected duration of hospitalization ≥6 days; Immobilization ≤3 days; NYHA III/IV HF; Acute respiratory failure, or at least one additional risk factor for VTE: acute infection without septic shock; acute rheumatic disorders; acute arthritis of the legs or an acute episode of RA in the legs; or an episode of IBD	Sixth day	6–14 days	LMWH 4000 IU once a day or 2000 IU once a day vs. placebo	N/A	N/A	14th day symptomatic or asymptomatic DVT and PE	N/A	[7]

rpth research & practice in thrombosis & haemostasis

TABLE 1 (Continued)

Randomized clinical trials

RCT	Indication for TP	Start of TP	Duration of TP	Class of anticoagulant/dose	RAM	Reassessment of risk of VTE	Outcome	Extended TP	Reference
PREVENT	Age >40 years; expected duration of hospitalization ≥4 days, acute congestive heart failure, acute respiratory failure, infection without septic shock, acute rheumatologic disorders, or IBD, presence of at least one risk factor for VTE; additional: age ≥75 years, cancer, previous VTE, obesity, varicose veins and/or chronic venous insufficiency, hormone replacement therapy, history of chronic heart failure, chronic respiratory failure, or myeloproliferative syndrome	First day	14 days	Dalteparin (LMWH) 5000 IU once a day vs. placebo	N/A	N/A	21st day symptomatic DVT, symptomatic PE, and asymptomatic proximal DVT and sudden death	If the patient was discharged before day 14, study medication was continued out of hospital	[8]
EXCLAIM	Age ≥40 years, life expectancy ≥6 months, Reduced mobility ≤3 days and at least one of the following conditions: NYHA III/IV HF, heart failure, acute respiratory, ischemic stroke, acute infection, acute rheumatological disease, inflammatory flare-up of chronic bowel disease, active cancer and at least one of the following conditions: age > 75 years, age ≥40 years, and history of VTE, age ≥40 years and active cancer or history of cancer	First day	10 ± 4 days in hospital	LMWH 4000 IU once a day vs. placebo	N/A	N/A	28th day VTE symptomatic or asymptomatic, proximal DVT, symptomatic PE, or fatal PE	28 days	[9]
LIFENOX	Age ≥40 years; expected duration of hospitalization ≥6 days, an ASA health status score of ≤3 (scale 1–6, with higher scores indicating more severe illness), acute cardiac decompensation, active cancer, severe systemic infection plus at least one of the following conditions: chronic lung disease, personal history of VTE, or age ≥60 years	Sixth day	6–14 days	LMWH 4000 IU once a day vs. placebo, and socks compression graduated elastic	N/A	N/A	All-cause mortality between the time of randomization and day 30	If the patient was discharged before day 14, study medication was continued out of hospital	[10]

TABLE 1 (Continued)

Randomized clinical trials

RCT	Indication for TP	Start of TP	Duration of TP	Class of anticoagulant/dose	RAM	Reassessment of risk of VTE	Outcome	Extended TP	Reference
ADOPT	Age ≥ 40 years, expected duration of hospitalization ≥3 days, moderate to severe mobility, cardiac insufficiency, accute breathing insufficiency, infection (without septic shock), acute rheumatic disease, IBD; except for patients with congestive heart failure or respiratory failure: age ≥75 years, previous VTE or history of VTE for which they have received anticoagulation for at least 6 weeks, cancer, BMI ≥30, estrogen hormone therapy, or chronic insufficiency heart or respiratory failure	1st day from randomization	Apixaban during 30 days vs. LMWH 6–14 days	Apixaban 2.5 mg twice a day vs. LMWH 4000 IU once a day	N/A	N/A	30th day DVT-related mortality, PE, DVT symptomatic/asymptomatic	30 days from randomization	[11]
MAGELLAN	Age ≥ 40 years, hospitalization ≤3 days before randomization, predictable rest ≥4 days, reduced mobility, NYHA III/IV HF, active cancer, ischemic stroke, acute infection, eruption of an inflammatory disease, acute breathing insufficiency and an additional risk factor for VTE: severe varicosis, chronic venous insufficiency, history of cancer, history of DVT/PE, history of HF (NYHA class III/IV), thrombophilia (hereditary or acquired), recent major surgery or serious trauma (6–12 weeks), hormone replacement therapy, advanced age ≥ 75 years, morbid obesity (BMI ≥35 kg/m²)	Up to 72 h after randomization	Rivaroxaban during 35 ± 4 days vs. LMWH 10 ± 4 days	Rivaroxaban 10 mg once a day vs. LMWH 4000 IU once a day	N/A	N/A	10th and 35th day symptomatic/asymptomatic DVT, symptomatic nonfatal PE, or VTE-related death	35 days from randomization	[12]

(Continues)

rpth research & practice in thrombosis & haemostasis

TABLE 1 (Continued)

Randomized clinical trials

RCT	Indication for TP	Start of TP	Duration of TP	Class of anticoagulant/dose	RAM	Reassessment of risk of VTE	Outcome	Extended TP	Reference
APEX	Age ≥40 years, had been hospitalized for <96 h for a specific acute medical illness (HF, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke) and had reduced mobility and specific risk factors for VTE: ≥75 years, or 60–74 years of age with D-dimer ≥2 ULN, or 40 through 59 years of age with D-dimer ≥2 ULN and a history of either VTE (DVT or PE) or cancer (excluding nonmelanoma carcinoma of the skin)	At least 96 h after hospitalization	Betrixaban during 35–42 days vs. LMWH 10 ± 4 days	Betrixaban 80 mg once a day vs. LMWH 4000 IU once a day	N/A	N/A	Between days 32 and 47 symptomatic DVT, symptomatic nonfatal pulmonary embolism or death from VTE between days 1 and 42	42 days	[13]
MARINER	Age ≥40 years and had been hospitalized for at least 3 and not more than 10 consecutive days with one of the following conditions: heart failure with a left ventricular ejection fraction of ≤45%, acute respiratory insufficiency or exacerbation of chronic obstructive pulmonary disease, acute ischemic stroke, or acute infectious or inflammatory disease, including rheumatic diseases; additional risk factors for VTE, according to IMPROVE ≥4; D-dimer level of more than twice the upper limit of the normal range; eligible patients must also have received thromboprophylaxis with LMWH or UFH during the index hospitalization	First day from randomization (on the day of discharge from the hospital)	45 days after hospitalization	Rivaroxaban 10 mg once a day or 7.5 mg once a day vs. placebo	IMPROVE	N/A	Symptomatic VTE or VTE-related death	45 days after hospitalization	[14]

for VTE receiving heparin (UFH or LMWH)[7–10] or direct oral antico-agulants (DOACs).[11–14] The MEDENOX,[7] EXCLAIM,[9] LIFENOX,[10] and PREVENT[8] RCTs compared enoxaparin[7,9,10] or dalteparin[8] with pla-cebo. The ADOPT,[11] MAGELLAN,[12] APEX,[13] and MARINER[14] studies compared apixaban with enoxaparin, rivaroxaban with enoxaparin, be-trixaban with enoxaparin, and rivaroxaban with placebo, respectively.

The RCTs that evaluated thromboprophylaxis with heparin in hos-pitalized patients showed discrepancies on parameters of efficacy outcomes.[7–10] For instance, the MEDENOX[7] and PREVENT[8] trials compared enoxaparin (4000 IU and 2000 IU once daily) or dalteparin (5000 IU once daily) with placebo for different periods: 6–14 days and 14 days, respectively. The EXCLAIM[9] trial compared enoxaparin (4000 IU once daily) with placebo for a period of 28 ± 4 days. Unlike the other trials, the LIFENOX[10] compared enoxaparin (4000 IU once daily) for 10 ± 4 days with placebo in patients using graduated elastic compression stockings.

The RCTs assessing the use of DOACs also showed different durations of the extended thromboprophylaxis. For instance, in the ADOPT trial,[11] apixaban (2.5 mg twice daily) was prescribed for 30 days; in MAGELLAN,[12] rivaroxaban 10 mg was prescribed once daily for 35 ± 4 days; in APEX,[13] betrixaban 80 mg once daily was used for 35–42 days; and in the MARINER[14] study, rivaroxaban 10 mg was prescribed once daily for 45 days.

The RCTs evaluating DOACs also showed differences regarding efficacy parameters when compared with the RCTs with heparin. In the RCTs with heparin, there is variability in the comparison between primary outcomes. In LIFENOX,[10] the primary outcome was death and not VTE. In the other three studies with heparin (MEDENOX,[7] PREVENT,[8] and EXCLAIM[9]), the primary outcome was the occur-rence of VTE, but with different outcome measures: In MEDENOX,[7] outcome was measured after 14 days, in PREVENT[8] at 21 days, and in EXCLAIM[9] in 28 days. In the RTCs with DOAC, the time to evalu-ate VTE efficacy outcome varied from 30 to 45 days: in ADOPT[11] it was 30 days, in MAGELLAN[12] 35 days, in APEX[13] 35 to 42 days, and in MARINER[14] 45 days.

Thus, we conclude that RCTs and guidelines addressing phar-macological thromboprophylaxis in hospitalized patients, although available for several years, do not use harmonized definitions, risk assessment models, or criteria for appropriate thromboprophylaxis. To advance the field, it is time for harmonization of these compo-nents in both guidelines and clinical trials.

AUTHOR CONTRIBUTIONS

BMF contributed to investigation, formal analysis, and writing the article. MB contributed to methodology, formal analysis, and writ-ing the article. SMR contributed to methodology, formal analysis, conceptualization, supervision, and writing the article. All authors revised and approved the final version of the manuscript.

FUNDING INFORMATION

RELATIONSHIP DISCLOSURE

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID

Bruno Ávila Ferreira https://orcid.org/0000-0003-0791-6153
Marcos de Bastos https://orcid.org/0000-0002-4158-1695
Suely Meireles Rezende https://orcid.org/0000-0002-3083-7093

TWITTER

Suely Meireles Rezende @facmedicinaufmg

REFERENCES

1. Wendelboe AM, Langenfeld H, Ageno W, et al. Current practices of standardized risk assessment for venous thromboembolism: results from a global survey from the World Thrombosis Day steering com-mittee. *J Thromb Haemost*. 2022;20:532-535.
2. 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.
3. Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P, Clinical Guidelines Committee of the American College of Physicians. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2011;155:625-632.
4. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e195S-e226S.
5. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous throm-boembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2:3198-3225.
6. National Institute for Health and Care Excellence: guidelines. Venous thromboembolism in over 16s: Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2018; 2018. https://www.nice.org.uk/guidance/NG89
7. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxa-parin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in medical patients with enoxaparin study group. *N Engl J Med*. 1999;341:793-800.
8. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medi-cal patients. *Circulation*. 2004;110:874-879.
9. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration ve-nous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med*. 2010;153:8-18.
10. Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann JF. Low-molecular-weight heparin and mortality in acutely ill medical patients. *N Engl J Med*. 2011;365:2463-2472.
11. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med*. 2011;365:2167-2177.
12. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for throm-boprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513-523.

13. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thrombo-prophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375:534-544.

14. Spyropoulos AC, Ageno W, Albers GW, et al. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. *N Engl J Med*. 2018;379:1118-1127.

15. Emed JD, Morrison DR, Des Rosiers L, Kahn SR. Definition of immobility in studies of thromboprophylaxis in hospitalized medical patients: a systematic review. *J Vasc Nurs*. 2010;28:54-66.

16. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8:2450-2457.

17. Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. *Chest*. 2001;120:1964-1971.

18. Ma KA, Cohen E, Kahn SR. Venous thromboembolism in hospitalized patients: an updated analysis of missed opportunities for thromboprophylaxis at a university-affiliated tertiary care center. *Vasc Med*. 2014;19:385-391.

19. 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.

20. MRR C, Nemeth B, Lijfering WM, Cannegieter SC. Validation of risk assessment models for venous thrombosis in hospitalized medical patients. *Res Pract Thromb Haemost*. 2019;3:217-225.