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STATE OF THE ART

# A systematic approach to venous thromboembolism prevention: a focus on UK experience

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## Abstract

Venous thromboembolism (VTE) remains a leading cause of preventable morbidity and mortality associated with hospitalization. Despite evidence that providing appropriate thromboprophylaxis to those at risk of VTE in hospital, recent data suggest that the delivery of thromboprophylaxis remains suboptimal across the globe, with a lack of standardization in approach to VTE prevention. This review considers the role of VTE risk assessment and interventions to improve the implementation of the VTE prevention pathway and highlights the systematic approach to VTE prevention adopted in England and its impact. Finally, the critical areas for further research and the emerging data presented during the 2022 ISTH annual congress in London, UK, are summarized.

**KEYWORDS**
anticoagulants, hospitalization, hospitals, morbidity, risk assessment, venous thromboembolism

**Essentials**

- Hospital-associated venous thromboembolism is a major patient safety issue.
- Provision of thromboprophylaxis to at-risk patients in hospital remains suboptimal.
- The introduction of a national VTE prevention programme, incorporating mandatory VTE risk assessment on admission, in England was associated with reduced post discharge VTE deaths.
- Further research to refine VTE prevention in medical patients and under-studied groups (nursing home residents, acutely ill psychiatry patients) is needed.

## 1 | INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), affects 1 in 1000 adults annually, [1] with the rate increasing to 1 in 100 in the elderly. [2] Up to 60% of all VTE cases are provoked by hospitalization, either during admission or within 90 days of discharge. [3–5] Furthermore, approximately 10% of hospital deaths are associated with PE. [6,7] Long-term VTE complications are an additional clinical and financial burden, with up to 20% to 50% of patients developing postthrombotic syndrome after proximal DVT [8] and 2.3% (95% CI, 1.5-3.1) developing symptomatic chronic thromboembolic pulmonary hypertension following PE. [9]

Hospital-associated-VTE (HA-VTE) is estimated to affect 10 million individuals annually, and was assessed as the leading cause of disability-adjusted life years (DALYs) lost, a measure of morbidity and mortality, in low- and middle-income countries, and second in

A state-of-the-art lecture, "Systematic approach to VTE prevention" was presented at the International Society on Thrombosis and Haemostasis congress in London, UK, in 2022.

high-income countries. Overall, HA-VTE was estimated to account for one-third of DALYs lost (7.7 million of 22.6 million DALYs lost) due to unsafe medical care, largely due to early death. [10] This likely underestimates the true burden as the modeling focused on inpatient events, and the majority of HA-VTE occurs postdischarge. [11] VTE prevention was recognized as a top clinical priority to improve patient safety in hospitals over a decade ago. [12] Despite good evidence to support thromboprophylaxis to prevent HA-VTE, implementation has proven to be more challenging. The VTE prevention pathway involves 4 steps as illustrated in Figure 1 [13]:

1. assess the patient's risk of VTE at admission (and when clinical condition changes),
2. counsel patient regarding VTE risk and how to reduce the risk,
3. prescribe appropriate thromboprophylaxis, and
4. administer appropriate thromboprophylaxis.

In this state-of-the-art review, we provide a brief overview of the role of VTE risk assessment and interventions to improve the provision of thromboprophylaxis; and highlight the systematic approach to VTE prevention adopted in England in 2010 and its subsequent impact before discussing the remaining challenges, priority areas for research, and relevant presentations at ISTH 2022, London, UK.

## 2 | VTE RISK ASSESSMENT

VTE risk assessment is the first and critical step in the VTE prevention pathway (see Figure 1). Several risk assessment models (RAMs) have been developed to enable targeted thromboprophylaxis to patients most likely to benefit from VTE thromboprophylaxis, thereby reducing potential harm to patients with low VTE risk (such as bleeding and heparin-induced thrombocytopenia) and improving cost-effectiveness. [14] However, there is uncertainty about which RAM is the most effective for use in clinical practice. The ideal RAM should be highly sensitive with optimal specificity, easy to use, widely applicable, cost effective, and incorporate the evaluation of bleeding risk. [15]

### 2.1 | Surgical patients

The American Society of Haematology (ASH) produced updated guidelines for VTE prevention in patients who underwent surgery in 2019; these guidelines ground recommendations for/against prophylaxis on the thrombotic and bleeding risk associated with the procedure with no further risk stratification based on patient characteristics. [16] This contrasts with earlier guidelines produced by the American College of Chest Physicians published in 2012 in which the importance of patient-specific risk factors were highlighted, with the Caprini score presented as a validated tool with use in clinical practice. [17] The Caprini score has been widely validated in numerous studies involving more than 250,000 patients. [18] Its characteristics are summarized in brief in the Table. [19–24] A meta-analysis of individualized risk assessment and VTE risk in surgical patients confirmed the utility of the Caprini score in risk stratification (13 studies including 14,766 patients). [25] Thromboprophylaxis reduced the risk of VTE by 40% to 60% in those with a Caprini score of 7 or more (score, 7-8; OR, 0.60; 95% CI, 0.37-0.97 and score >8; OR, 0.41; 95% CI, 0.26-0.65), whereas no significant reduction in VTE risk was seen in patients with scores of ≤6 (representing 75% of the patient cohort). This suggests that recalibration of the threshold for thromboprophylaxis may improve targeting of the at-risk population and cost-effectiveness. [25]

### 2.2 | Medical patients

Although the Caprini score was developed for surgical patients, it has also been evaluated in medical patients. VTE risk factors and outcomes were collated from 63,548 non–critically ill medical patients across 48 hospitals in the United States between 2011 and 2014. [26] Investigators reported that the Caprini RAM was linearly associated with VTE risk up to a score of 10, with thromboprophylaxis reducing the risk of VTE by 15% (OR, 0.85; 95% CI, 0.72-0.99). However, as only 1.05% of patients developed VTE within 90 days of hospital admission, the Grant et al. highlighted that large numbers are needed

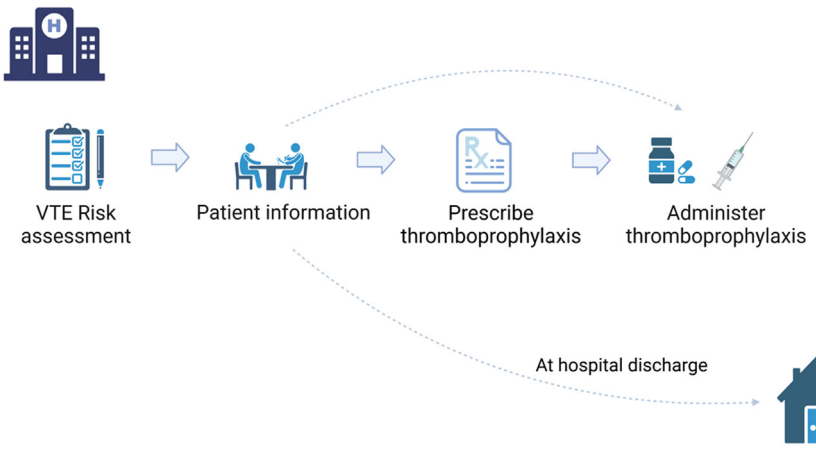


**FIGURE 1** Visual representation of the VTE prevention pathway. *Source*: Adapted from Ariëns et al. [13] with permission from Wiley. VTE, venous thromboembolism

**TABLE** Comparison between commonly used risk assessment models for hospitalized acutely ill medical patients.

| RA model | External validation | Target patient population | Risk factors, *n* | Weighting of risk factors | Score at which thromboprophylaxis is indicated | % Patients deemed high VTE risk [19] | Bleeding RA |
|---|---|---|---|---|---|---|---|
| Caprini [20] | Yes | Medical and surgical | 39 | Yes | ≥5 | 82 | No |
| Department of Health, England [21] | No | Medical and surgical | 19 | No | ≥1 | 80 | Yes |
| IMPROVE [22] | Yes | Medical | 7 | Yes | ≥3 | 48 | Yes[a] |
| Padua Prediction Score [23] | Yes | Medical | 11 | Yes | ≥4 | 32 | No |

RA, risk assessment; VTE, venous thromboembolism.
[a]A separate IMPROVE bleeding risk assessment is available [24].

to be treated to prevent a single VTE event. [26] An optimal threshold for thromboprophylaxis could not be identified, although other analyses suggest cost-effectiveness with a VTE risk threshold of 1% [27] (corresponding to a Caprini score of 5 or more in this study). [26]

ASH guidelines for the prevention of VTE in medical patients do not include recommendations for VTE risk assessment but review both Padua and IMPROVE scores. Furthermore, the guidelines suggest that clinicians and health care systems incorporate VTE and bleeding risk assessments in their application of VTE prevention guidelines to optimize appropriate thromboprophylaxis delivery, reducing the risk of bleeding in those at low risk of VTE and increasing cost-effectiveness. [14] The characteristics of these RAMs are summarized in the Table. A recent systematic review of 51 studies aimed at comparing the accuracy of RAMs in predicting VTE in hospitalized patients found that the evaluation focused more commonly on medical patients (21 studies), with Caprini (22 studies), Padua (16 studies), and IMPROVE (8 studies) being the most widely studied tools. [28] The authors highlight wide variation in study design, implementation of RAMs, outcome definition, and thromboprophylaxis, with 23 studies not reporting on thromboprophylaxis use. There was thus insufficient evidence to identify an optimal RAM for clinical use. [28] This supports the findings of an earlier systematic review focused on patients who were medically ill. [15] There is, therefore, a need for pragmatism in selecting a VTE RAM (at the site or national level) as the initial step for appropriate VTE prevention.

## 3 | INTERVENTIONS TO IMPROVE THE PROVISION OF THROMBOPROPHYLAXIS

### 3.1 | Implementation of VTE prevention guidelines

Multiple societal bodies have published guidelines on VTE prevention in hospitalized patients—most recently the American Society of Haematology [14,16] and the National Institute for Care and Health Excellence. [29] These guidelines present a comprehensive analysis of the evidence for thromboprophylaxis, which is not further reviewed here.

There has been limited study of the impact of the implementation of VTE prevention guidelines. A meta-analysis identified only 4 small studies evaluating this in medical patients and found that guideline implementation led to improved, but still suboptimal, provision of appropriate thromboprophylaxis (with rates of 31%-72% post-implementation). [30]

A systematic review and meta-analysis examined the effectiveness of system-wide interventions to improve thromboprophylaxis provision and reduce symptomatic HA-VTE. [31] It identified 13 studies involving 35,997 patients and reported that the use of human and/or electronic alerts improved appropriate thromboprophylaxis prescription by 16% (95% CI, 12-20) and reduced HA-VTE by 36% (relative risk [RR], 0.64; 95% CI, 0.47-0.86). In contrast, multipronged interventions, including education and training, had a lesser 4% (95% CI, 2-11) increase in the provision of thromboprophylaxis. Electronic alerts were superior to human alerts and additionally enhanced the impact of a multipronged approach.

### 3.2 | Patient education

Patient awareness of VTE and the risk of HA-VTE remains low in comparison with arterial disease as highlighted by an international study of 7233 lay participants in 9 countries. [32] Lower awareness of DVT and PE was seen in comparison with other thrombotic conditions such as myocardial infarction and stroke. [32] Furthermore, only 45% (95% CI, 43.9-46.5) were aware that VTE was preventable and had limited awareness of the associated risk factors. [32] Counseling patients regarding their VTE risk is therefore critical to ensure adherence to thromboprophylaxis. Additionally, as the majority of patients develop VTE following discharge, [3,5,33] patient information to raise awareness of symptoms and to encourage them to seek early medical review in their event is crucial.

Nonadministration of thromboprophylaxis is frequent, with a retrospective review of >100,000 ordered thromboprophylaxis doses reporting that 11.9% were not administered, with 59% of omitted doses because of patient refusal. [34] A smaller study of 250 patients, which prescribed prophylactic unfractionated heparin (UFH) 2 or 3 times daily

and low molecular weight heparin (LMWH) once daily, reported that patients prescribed with LMWH more frequently received all prescribed doses (77% compared with UFH 45% to 54% depending on frequency prescribed) but with a similar proportion of missed doses due to patient refusal (UFH, 44%; LMWH, 39%). [35] Both nurse and patient education are effective in reducing thromboprophylaxis dose omissions. [35,36] A recent single-center, cluster-randomized controlled trial involving 11,908 patient visits found interventions such as alerts for patient-centered education and nurse feedback reduce thromboprophylaxis dose omissions (from 13.4% to 9.2%; OR, 0.64; 95% CI, 0.57-0.71), with patient-centered educational interventions being more effective. [37]

A survey of 227 (from 421 invited) patients/caretakers identified via patient groups in the United States (the North American Thrombosis Forum, the National Blood Clot Alliance and Clot Care, and the Johns Hopkins Hospital Patient and Family Advisory Council) indicated that patients will accept education via a variety of methods, with the doctor–patient interaction being the preferred means. [38] Of note, this was a highly selected cohort with the majority of participants having a personal or family history of VTE.

The EMPOWER study in patients receiving systemic anticancer therapy demonstrated the use of a patient information video regarding the risk of VTE significantly reducing the time to presentation with symptoms from 8.9 to 2.9 days (95% CI, 4.5-7.4; hazard ratio [HR], 0.33). [39] Given the majority of HA-VTE occur post–hospital discharge, strategies to enhance the delivery of patient information at discharge warrant further evaluation. Efforts should be made to ensure that all patients receive information in some form at the time of hospital discharge.

The "World Thrombosis Day" global awareness campaign was launched by the International Society on Thrombosis and Haemostasis, in 2014. In 2021, the campaign reached over 6.1 billion people, a 17% increase from 2020, with more than 3000 partners in 130 countries. [40] Further international studies led by the World Thrombosis Day steering committee are discussed in Section 5.

## 4 | SYSTEMATIC APPROACH TO VTE PREVENTION IN ENGLAND

In England, a national VTE prevention program was launched in 2010, with the primary aim of reducing preventable harm, morbidity, and mortality secondary to hospital-associated VTE. [41] The secondary aim was to embed the best VTE prevention practice into routine care. The program hinged on the introduction of mandatory documented VTE risk assessment with centralized reporting and a financial penalty for failing to achieve >90% VTE risk assessment rates (at launch, increased to 95% in 2014). Additional supports included a bespoke national VTE risk assessment tool, [22] national NICE VTE prevention guidelines, [29,42] development of a National VTE Exemplar Centre network, and the National Nursing and Midwifery Network.

The national VTE risk assessment rate increased steadily from 47% in July 2010 to >90% in November 2011 (see Figure 2) and has been maintained above target until the last reporting period (December 2019). [41] In 2015, postdischarge VTE deaths (within 90 days of hospital discharge) were introduced into the NHS outcomes framework, providing the first national VTE prevention outcome indicator. Postdischarge VTE deaths reduced by 16.2% from 2007/2008 to 2019/2020 (Figure 3). [43] Although both metrics are highly reassuring, there were little national data on other process/outcome indicators. This led to the development of a National Thrombosis survey, in conjunction with the *Getting It Right First Time* (GIRFT) national quality improvement program. [44] All NHS hospitals were invited to contribute data to 3 electronic surveys from October 2019 to March 2020:

1. Organizational approach and resource for VTE prevention;
2. Patient-level survey of VTE prevention care provided;
3. Patient-level survey of VTE prevention care in patients who developed HA-VTE. [44]

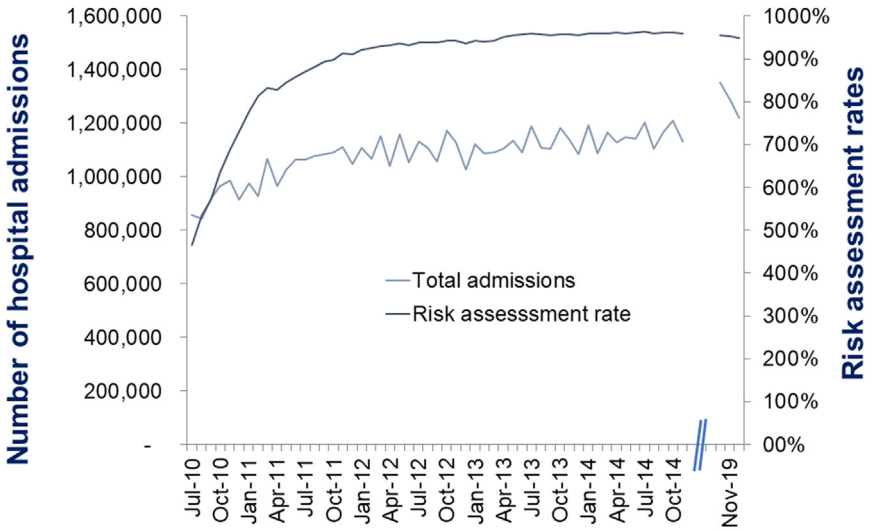


**FIGURE 2** Hospital admissions and VTE risk assessment rates in England. Data available from: https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/venous-thromboembolism-vte-risk-assessment-collection. [accessed September 7, 2022]. VTE, venous thromboembolism

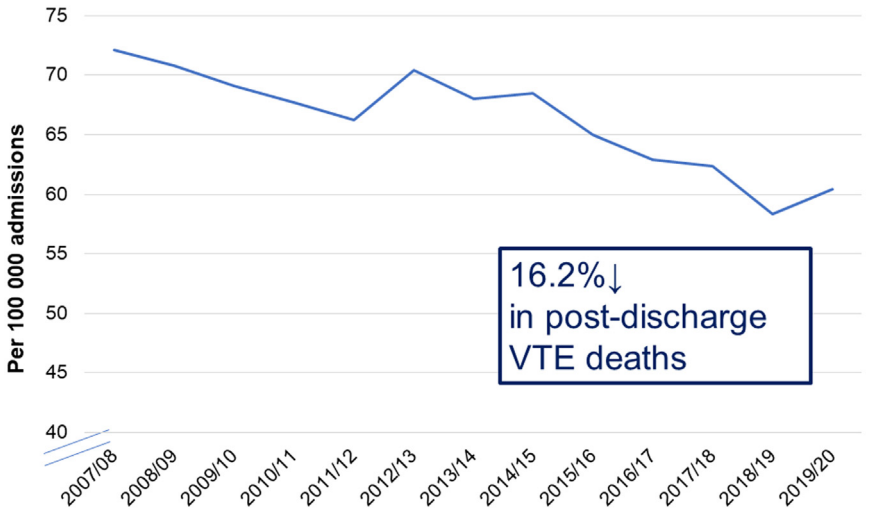


**FIGURE 3** Deaths from VTE-related events within 90 days post hospital discharge in England, per 100,000 admissions; 2007/2008 to 2019/2020. Data available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-outcomes-framework/february-2021/domain-5-treating-and-caring-for-people-in-a-safe-environment-and-protecting-them-from-avoidable-harm-nof/5.1-deaths-from-venous-thromboembolism-vte-related-events-within-90-days-post-discharge-from-hospital. [accessed September 7, 2022]. VTE, venous thromboembolism

Of 144 NHS Trusts, 98 (67%) contributed to one or more surveys. These confirmed that most hospitals (87%) continued to use the NHS VTE risk assessment tool and that prescription rates of appropriate thromboprophylaxis were high (88% of $n$ = 7399). There was, however, significant variation in prescription rates between hospitals of 40% to 100%, with 8% of patients having inappropriate dose omissions of pharmacologic prophylaxis. The survey also highlighted that only 31% (of $n$ = 9553) had evidence of the provision of patient information regarding VTE risk. Of 4595 episodes of HA-VTE submitted, 13% of them were considered potentially preventable due to omissions in VTE prevention care at each point in the pathway, eg, incorrect, delayed, or lack of VTE risk assessment; failure to reassess VTE risk when clinical condition changed; lack of, or delayed anticoagulant prescription or use of an incorrect dose for body weight; and/or missed doses or patients declining thromboprophylaxis. [44] As expected, given thromboprophylaxis reduces (but does not eliminate) VTE risk, a significant proportion of HA-VTE (45%) occurred despite optimal thromboprophylaxis. The report provides 13 recommendations aimed at both hospitals and arm's length bodies within the United Kingdom to further integrate and improve VTE prevention and proposes a repeat survey to evaluate the impact. All participating hospitals were provided with a site-specific pack enabling benchmarking of performance with other participating hospitals. Ongoing drivers to improve practice in England include an updated NICE quality standard published in 2018; this recommends an audit of the proportion of patients admitted with thromboprophylaxis prescribed within 14 hours of admission and includes the rate of HA-VTE as an outcome indicator.

The central reporting of VTE risk assessment rates was paused in 2020 with the advent of the COVID pandemic; it remains within the NHS Standard contract but is uncertain when/whether data collection will resume. HA-VTE and its prevention features in the new NHS Patient Safety Strategy and is additionally highlighted as a current research need. [45]

## 5 | COMPARISON TO A GLOBAL APPROACH

Across the globe, there is greater variation in approach; Wendelboe et al. [46] collated responses on the national approach to VTE prevention from 223 ISTH members/attendees at the 2019 ISTH meeting, representing 34 countries. The United Kingdom was one of only 3 countries with good uptake of mandatory VTE risk assessment and national VTE prevention guidelines. A systematic review and meta-analysis of the global use of RAMs and thromboprophylaxis in acutely ill medical patients admitted to hospital found that 55% received appropriate thromboprophylaxis. [47] Although this is improved on the 40% appropriate thromboprophylaxis rate reported by the ENDORSE study, [48] it falls considerably below target and the rate (88%) reported in the GIRFT Thrombosis Survey. [44] Additionally, it highlights variation across continents, with the lowest rate of appropriate use in Asia (<40%) and the highest in Europe and North America (>65%). The Caprini and Padua RAMs were the most commonly used in the included studies. [47]

## 6 | CHALLENGES

### 6.1.1 | Measuring the optimal outcome indicator

Outcome monitoring of VTE prevention is time-intensive; screening radiology reports and linking back to admission data were the most effective strategies identified in the GIRFT Thrombosis Survey. [44] This requires investment in staff (or technology) and likely contributes to observations of higher HA-VTE rates in hospitals with higher standards of VTE prevention, due to surveillance bias associated with increased awareness and investigation for VTE. [39,49] Falling rates of autopsy likely contribute to the underreporting of deaths due to HA-VTE, as many such events are not clinically suspected. [7] However, within single systems, there is likely to be little variation over time, and outcome

monitoring is useful both to demonstrate the impact of interventions, and also to identify areas in need of further attention. Future automated means for the detection of VTE using artificial intelligence/machine learning warrants further investigation. [50]

### 6.1.2 | Environmental impact

A recent commentary highlighted the carbon footprint of heparin, with 1.1 billion pigs slaughtered annually for heparin production. [51] The global porcine industry emits 668 million tons of carbon dioxide per annum. Although it is laudable that 80% of the pharmaceutical industry have agreed to reduce their carbon footprint with net zero targets, this will be difficult to achieve with the current demand and use of heparin. This is an additional driver for appropriate heparin use with risk assessment strategies integral to targeting thromboprophylaxis to those most likely to benefit, thereby improving cost-effectiveness and minimizing the environmental impact. Additionally, available alternatives, such as direct oral anticoagulants following major orthopedic surgery, should be used appropriately. Fondaparinux is an attractive, but currently, more expensive alternative in other hospitalized patients. The pipeline of factor XI inhibitors holds promise, and the ongoing evaluation of these agents will hopefully deliver safer and ecofriendly alternatives to heparin. [52]

### 6.1.3 | Gray areas

VTE is common among nursing home residents, accounting for 13% of patients with VTE in Sweetland et al.'s [4] population cohort study. The reported incidence of VTE associated with care home residence ranges from 0.7 to 3.8 per 100-patient years, with autopsy data suggesting that this represents a significant underestimation. [53–55] A retrospective study suggests an increased VTE risk early after nursing home admission with ~40% of all events diagnosed in the first 4 weeks. [56] The high incidence particularly shortly following admission suggests a need for randomized controlled trials to establish the role of thromboprophylaxis in abrogating this risk. [51] Acute psychiatry admissions were highlighted in the updated NICE guidelines, with a call for risk assessment on the admission of all acute psychiatry patients. [29] There are very limited data regarding VTE incidence and risk stratification in this setting [57] and, therefore, a pressing need for research to define VTE risk associated with psychiatric admission and to evaluate the role and acceptability of thromboprophylaxis. Rehabilitation settings may also be associated with increased VTE risk, but again there is a lack of robust data to inform best practices.

## 7 | ISTH CONGRESS REPORT

During the 2022 ISTH Congress, several abstracts were presented relating to VTE risk assessment in hospitals, education, and implementation of VTE prevention. Two abstracts focusing on the utility of the Department of Health VTE RAM were also presented. In a prospective, single-center observational cohort, they found a substantial inter-rater agreement for VTE risk assessment in medical patients (Cohen's Kappa [κ], 0.75; 95% CI, 0.64-0.86) with only moderate inter-rater agreement in patients who underwent surgery (κ, 0.56; 95% CI, 0.36-0.75). [58] A further study compared 6 VTE RAMs and reported the proportion of patients ($n$ = 274) for whom the RAM recommended thromboprophylaxis; there was wide variation in the proportion requiring thromboprophylaxis from 11% to 91% (with the Department of Health tool identifying the highest proportion of patients as high VTE risk). [59] An external validation of the Intermountain RAM for postdischarge HA-VTE in a retrospective cohort of 113,578 patients reported poor discrimination in identifying those at risk of post-discharge HA-VTE (1.1% in high risk vs 0.6% in low risk) but good discrimination for bleeding risk (1.3% high vs 0.1% low bleeding risk); 14.5% of the cohort had high VTE and low bleeding risk. It was proposed that this cohort should be evaluated for extended thromboprophylaxis in future studies. [60] A single-center retrospective external validation of the IMPROVE RAM ($n$ = 23,911) reported poorer performance (AUC, 0.64) in comparison to the derivation study. [61] The authors also presented the derivation and external validation of a new VTE RAM comprising 11 risk factors available within 24 hours of hospital admission, for which further external validation is in progress. [62]

A single-center pilot cluster-randomization study randomizing wards to standard thromboprophylaxis or a multipronged intervention including a clinical decision support system reported that the multipronged intervention improved VTE thromboprophylaxis provision, with an unexpected increase in HA-VTE in both the groups. [63] A case-based interactive education model for VTE prevention in infectious diseases was evaluated and demonstrated improved clinician competence in 83% (of 183 participants). Further study of the clinical impact of educational interventions is required. [64]

## 8 | FUTURE DIRECTIONS

Given that a significant number of HA-VTE occur despite optimal thromboprophylaxis, there is an urgent need to better identify patients at risk of VTE to enable individualized thromboprophylaxis. Improved risk stratification will facilitate randomized controlled trials of intensified and/or extended thromboprophylaxis regimens for patients at very high VTE risk. Additionally, the seminal studies of thromboprophylaxis [65,66] may not apply to admitted patient cohorts today with postoperative enhanced recovery programs and significantly shorter lengths of stay for both medical and surgical patients. In medical patients, the randomized controlled trials of LMWH-targeted patients with distinct comorbidities (including heart failure, acute respiratory failure, acute infection, and acute rheumatologic conditions), and predicted length of stay of at least 4 to 6 days. [65,66] This contrasts with the median 3-day length of stay for medical patients in England (pre-COVID, after excluding day cases). [67] Recognition of the increasing use of thromboprophylaxis in unselected

medical patients has led to calls for further randomized controlled trials of thromboprophylaxis in hospitalized acutely ill medical patients. [68]

The World Health Organization (WHO) includes the prevention of HA-VTE as a key component for ensuring safety of clinical processes in their Global Patient Safety Action Plan (2021-2030). [69] WHO proposes the use of mandatory VTE risk assessment at hospital admission to drive optimization of VTE prevention and monitoring of avoidable VTE-associated deaths as the outcome indicator. At a special ISTH–WHO session, Dr Neelam Dhingra highlighted ISTH World Thrombosis Day Steering Committee's ambitious goal of mandatory VTE risk assessment on hospital admission in 90% of all countries by 2030. Recognition by the WHO of VTE as a major contributor to the burden of preventable noncommunicable disease provides an essential driver to achieving this aim globally.

## 8 | CONCLUSIONS

HA-VTE is a common and potentially devastating complication of hospitalization. A systematic approach to VTE prevention, such as that implemented in England significantly improves the use of thromboprophylaxis and reduces mortality associated with HA-VTE. The pragmatic use of a universal VTE risk assessment tool is the key to successful implementation, and the inclusion of this in the WHO patient safety agenda represents a useful global driver. Further research to elucidate optimal approaches to VTE prevention in medical patients (and other understudied groups such as acutely ill psychiatry patients and nursing home residents) is required.

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Both R.E.C. and L.N.R. wrote the manuscript.

### RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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