New paradigms in venous thromboprophylaxis of medically ill patients

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Summary

Acute-ill hospitalised medical patients are at risk of venous thromboembolism (VTE), both in-hospital and in the immediate post-discharge period, and mortality from VTE is thought to be particularly high in this patient population. However, despite previous mandates from international antithrombotic guidelines such as those of the American College of Chest Physicians (ACCP) for the “universal” use of thromboprophylaxis in hospitalised medical patients, global audits suggest that implementation of thromboprophylaxis continues to be challenging because of the perceived higher risk of bleeding and lower risk of VTE than that reported in clinical trials. Recent population-based studies also reveal that a “universal” hospital-only thromboprophylactic strategy does not reduce the community burden of VTE from this population, which may constitute nearly one quarter of the attributable risk of VTE. Lastly, four large randomised placebo-controlled trials of extended thromboprophylaxis have failed to show a definitive net clinical benefit in hospitalised medical patients. Recent large-scale efforts in deriving and validating scored VTE and bleed risk assessment models (RAMs) have been completed in the medically-ill population. In addition, an elevated D-dimer as a new biomarker to identify at-VTE risk medically ill patients has also undergone prospective evaluation. This paper will review current concepts of VTE and bleed risk in hospitalised medical patients, both in the hospital as well as the post-hospital discharge period, and will discuss new paradigms of thromboprophylaxis in this population using an individualised, patient-centered approach.

Keywords

Medical patient, risk assessment models, d-dimer, venous thromboembolism, bleeding, thromboprophylaxis, Padua Score, NHS Tool, IMPROVE Score, low-molecular-weight heparin, direct oral anticoagulants

Introduction

There are an estimated 8 million and 12 million acutely-ill hospitalised medical patients annually in the US and EU, respectively (1, 2). Venous thromboembolism (VTE) remains a significant cause of morbidity and mortality in this population, with hospitalisation for medical illness accounting for almost one quarter of the incident VTE events occurring in the community (3). The mortality due to pulmonary embolism (PE) is thought to be particularly high among hospitalised medical patients. In addition, the immediate post-hospital discharge period remains a particularly vulnerable period of VTE risk in this population (4).

The rationale for thromboprophylaxis in hospitalised medical patients is based on the high incidence and clinically silent nature of VTE in this patient population, its associated morbidity and mortality, and results of randomised controlled trial data with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux that have firmly established the effectiveness and a net clinical benefit with short-term in-hospital use of these agents (5, 6). However, despite clear mandates for the “universal” use of thromboprophylaxis in hospitalised medical patients from international antithrombotic guidelines such as those of the American College of Chest Physicians (ACCP) (7), implementation of thromboprophylaxis in the medically ill continues to be challenging because these patients tend to be older, suffer from multiple comorbidities, and receive medications that may interact with prophylactic therapies for VTE (8, 9). Global audits have shown underutilisation of thromboprophylaxis by clinicians in hospitalised at-risk medical patients, mainly due to the perceived higher risk of bleeding or lower risk of VTE than that reported in the clinical trials (10). More recently, large population-based studies in medically ill suggest that use of a “universal” in-hospital – only thromboprophylactic strategy does not reduce the community burden of VTE in this population (11, 12). Lastly, although the post-hospital discharge period remains a high VTE risk period in hospitalised medical patients, four large placebo-controlled trials of extended thromboprophylaxis with either LMWH or the direct oral anticoagulants (DOACs) and comprising of over 28,000
medical patients have failed to show a definitive net clinical benefit in this setting, due mainly to uncertainty about a benefit in reduc-
ing fatal PE, and rates of major bleeding that are perceived to be
too high (13, 14).

This paper will review current concepts of VTE and bleed risk in hospitalised medical patients, both in the hospital as well as the post-hospital discharge setting, and discuss new paradigms of thromboprophylaxis in this population. We will attempt to syn-
thesise both existing data as well as evolving strategies to provide a framework for both VTE and bleed risk assessment and thrombo-
 prophylaxis using a patient-centered approach.

Periods of venous thromboembolic risk in the medically ill

There are three periods of VTE risk in hospitalised medically ill patients that are helpful to conceptualise from a perspective of both VTE risk as well as utility of a thromboprophylactic strategy:

- The acute hospitalisation period (~ 6–14 days) – this likely repre-
sents an at-VTE risk period that is tied to a patient’s immobility
and disease severity, usually from an acute on chronic medi-
cal illness exacerbation.

- The post-hospital discharge period (up to 45 days) – this likely
represents a high VTE risk period and is related to both dis-
eaese-specific exacerbation of a patient’s underlying illness as
well as patient-specific VTE risk factors. Although the period of
VTE risk may extend up to 90 days post-discharge, the majority
(~80%) of VTE events occur in the first 45 days after hospital
discharge.

- Chronic medical illness phase – which long-term VTE risk is
tied to a chronic medical condition.

Both exposing (disease-specific) and predisposing (patient-specific)
risk factors for VTE in acutely-ill medical patients may contribute
to a patient’s overall risk for VTE, although not all risk factors are
weighed the same in contributing to this risk. Medical illness in-
cluding ischemic stroke, congestive heart failure (CHF), chronic
obstructive pulmonary disease (COPD), acute infectious disease,
and inflammatory bowel and rheumatic disease have all been as-
associated with increased risk of VTE (5, 15). A group of approxi-
mately 15 patient specific risk factors, including personal history
of VTE, advanced age, cancer, and congenital or acquired throm-
bophilia have been shown to be significantly associated with VTE in
the medically ill population (6). More recently, VTE risk assess-
ment models (RAMs) in hospitalised medical patients have con-
sistently identified a list of patient-specific risk factors, including
advanced age, immobility/bed rest, known thrombophilia, active
or recent cancer, prior VTE, and current limb paralysis, as inde-
pendent risk factors for VTE (16, 17).

The acute hospitalisation period (~ 6–14 days)

The incidence of DVT has been reported to range from 10% to
26% among general medical inpatients (18, 19). Most of the DVT
are asymptomatic. DVT is estimated to occur in approximately
55% of patients with a recent history of stroke and patients with
congestive heart failure or COPD are at increased risk for both de-
velopment of VTE and death following PE (20, 21). Although the
lack of symptoms and low autopsy rates make it difficult to deter-
mine the exact incidence of fatal PE among this patient group,
autopsy and longitudinal studies report anywhere from a 2.5% to
7.6% incidence of autopsy-proven fatal PEs (22, 23) and have
shown that approximately 75% of fatal PEs occur in non-surgical
hospitalised patient populations (24–26).

Older randomised trials with UFH in hospitalised medical pa-
tients based on mortality endpoints have revealed a significant
~30% risk reduction in all cause mortality and time from randomi-
misation to fatal PEs in favor of UFH (27, 28). More recent place-
bo-controlled trials with LMWH and the pentasacharide fondaparinux using venographic or ultrasonographic endpoints have re-
vealed a significant 50%–60% reduction of VTE favoring a 6 to
14 day duration of pharmacologic therapy in this population (29)
(30, 31). Meta-analyses of in-hospital thromboprophylaxis of
medical patients have revealed a ~60% reduction in any PE and
fatal PE, and non-significant reductions in DVT (32). Anticoagul-
ant prophylaxis had no effect on all-cause mortality (relative risk,
0.97 [CI, 0.79 to 1.19] (32).

The post-hospital discharge period (up to 45 days)

Recent epidemiologic data suggest that the period of VTE risk in
medically ill patients extends well beyond their hospital admission
period, up to 90 days after their hospital discharge, with the major-
ity of events occurring in the first 45 days after index hospitali-
sation (4, 33). In the IMPROVE registry of 15,156 patients, the
median time for all VTE events was 17 days (interquartile range
6–43 days), and the median time for post-discharge VTE events
was 44 days (interquartile range 25–68 days) (4). In the US Hospi-
tal Performance Consortium for VTE of 20,994 patients, 85% of
all VTE events occurred in the post-discharge period (12). The
rate of symptomatic VTE in medically ill more than doubles over
the first 21 days post-discharge and is associated with a five-fold
increased risk of fatal PE within 30 days post-hospital discharge
(4). Large population data including a US claims database of over
141,628 medical patients consistently reveal that a small percen-
tage of this patient group (<4.0%) receives routine post-discharge
thromboprophylaxis (11).

There have been four large clinical trials of extended versus
short duration thromboprophylaxis in acutely-ill hospitalised
medical patients with either LMWH or the DOACs (rivaroxaban,
apixaban, betrixaban) comprising over 28,000 patients (34, 35)
(36, 37). Although the relative risk reduction (RRR) in ultrasono-
graphic DVT was modest (~25%) in the extended therapy groups
at ~35 to 42 days, extended thromboprophylaxis was associated
with a more robust decrease in symptomatic proximal or distal
DVT [Relative Risk (RR) = 0.52, 95% CI 0.35–0.77] and sympto-
matic non-fatal PE [RR = 0.61, 95% CI 0.38–0.99] (38). However,
with the exception of the APEX trial with betrixaban, this was off-
set by an approximate two-fold increase in major bleeding [RR =
2.08, 95% CI 1.50–2.90], thus failing to show a definitive net-clinical benefit of extended thromboprophylaxis (14, 38).

Uncertainty regarding the true relationship between asymptomatic and symptomatic VTE, the recent emphasis in antithrombotic guidelines such as those of the ACCP towards more patient-centric outcomes (including symptomatic and fatal VTE), and a deeper appreciation of the silent nature and severity of VTE in elderly, co-morbid patients with limited cardiopulmonary reserve – such as those with acute medical illness – all have contributed towards a shift in our understanding of recent antithrombotic prophylaxis studies of medically ill patients (39). A reduction in symptomatic VTE, and importantly VTE-related death, would constitute high quality evidence of benefit, and a risk-benefit trade-off emphasizing symptomatic VTE and bleeding would constitute a high level of confidence in recommendations of antithrombotic prophylaxis (39). It is important to note that the absolute rate of fatal VTE in studies of extended thromboprophylaxis of medically-ill (0.2% to 0.3%) was an order of magnitude greater than the rate of fatal bleeds (0.03 to 0.06%)(14).

Chronic medical illness

There likely remains a small proportion of medically ill patients, especially those who are elderly and bedridden and those with chronic severe CHF, that may benefit from a strategy of long-term primary thromboprophylaxis. Despite the substantial risk of VTE in chronically-ill elderly medical patients, there is evidence of suboptimal VTE prophylaxis in this population. Reasons of inadequate prophylaxis include incorrect assessment of VTE risk, fear of bleeding, and lack of awareness and specificity of clinical guidelines (40). The DEPART epidemiologic study conducted over 17 years ago confirmed that LMWH for primary thromboprophylaxis was given to as many as 44% of elderly bedridden medical outpatients without acute illness, suggesting both overuse in this patient population but at the same time an unmet medical need in risk stratifying medical outpatients at risk for VTE (41).

Limitations of the established paradigm of “universal” thromboprophylaxis for acutely ill medical patients

The current strategy of “universal” or “group-based” primary thromboprophylaxis of medically-ill patients, including those with CHF, severe lung disease, ischaemic stroke, cancer, acute infection, and rheumatologic disease, begun at the time of admission and continued for the duration of stay in hospital, has failed to reduce the burden of VTE in the community (11, 12, 42, 43). This is likely due to a number of factors, including: 1) the shortening length of hospital stays that have potential to dampen the treatment effect of in-hospital thromboprophylaxis, 2) the lack of routine use of thromboprophylaxis in the post-hospital discharge period to achieve the minimum duration of VTE prophylaxis as established by the clinical trials, and 3) the potential for a “universal” thromboprophylactic strategy to emphasise inappropriate pharmacologic VTE prevention in low-risk medically ill patients and not place enough emphasis in high-risk patients (either by insufficient intensity or duration of thromboprophylaxis) (11, 12), resulting in an unfavorable risk-benefit impact on the population. In addition, the high screening-to-recruitment ratios and the inclusion of patients with additive VTE risk factors in many of the thromboprophylaxis trials may have limited the external generalisability and interpretation of trial results in the use of pharmacologic prophylaxis across a broad group of general medical inpatients. It was for these reasons that recent international antithrombotic guidelines such as those from the 9th Edition of ACCP, have for the first time moved away from a “universal” or “group” based strategy of prophylaxis in the hospitalised medical patient towards an individualised approach of both a patient’s VTE as well as bleed risk when determining an appropriate thromboprophylactic strategy (44).

Individualised (patient-level) thromboprophylaxis for medically ill patients at hospital admission using risk assessment models

A recent systematic review identified a number of VTE RAMs that have been derived in hospitalised acutely ill medical patients (16). Of these, only the Padua VTE RAM and the IMPROVE VTE RAM, which consist of weighted and scored risk models based on patient- and disease-specific VTE risk factors, have gone through extensive external validation, while the UK National Health Service (NHS) Tool has gone through extensive outcomes assessment (4, 45-49). The Padua VTE RAM used an 11-factor model from 1–3 points in a binary fashion: high risk of VTE was designated with a score of 4 or more warranting pharmacologic prophylaxis, and low VTE risk was designated with a score < 4 (Table 1) (45). The evidence-derived IMPROVE VTE RAM utilised seven clinical risk factors that were independently associated with VTE risk in a global registry of 15,125 medically-ill patients (50). The model used 1–3 points to designate three tiers of VTE risk: low VTE risk (symptomatic VTE < 1.0%) designated with a score of 0–1, at-risk (or moderate VTE risk) with a VTE event rate of ~1.0–1.5% designated with a score of 2 to 3, and high VTE risk with a VTE event rate of 4% or more designated with a score of 4 or more (Table 2) (4). The IMPROVE VTE RAM had good discrimination and calibration characteristics when studied in two large external validation studies comprising of nearly 40,000 patients, with area under the receiver operating characteristic (ROC) curve of 0.77 and 0.70 (47, 48). The UK NHS Tool, as part of a national quality initiative to increase the number of surgical and non-surgical patients screened for VTE risk to at least 90% – linked to a financial penalty – resulted in a significant reduction in death from VTE at 90 days after hospital admission (RR 0.85, 95% CI 0.75–0.96; p = 0.011) (49).

All of the clinical VTE RAMs in the medically-ill population, including the Padua and IMPROVE VTE RAM, suggest that we are committing two errors when instituting a “universal” or “group-specific” health-systems wide thromboprophylactic strategy, as had previously been suggested by antithrombotic guide-
lines. The VTE RAMs consistently (with negative predictive values of ~99%) point to the fact that only about 35–50% of the medically ill population are at sufficient VTE risk to warrant pharmacologic thromboprophylaxis, using a symptomatic VTE event rate of 1.0% as the clinical threshold suggested by the ACCP guidelines by which benefits of a pharmacologic approach may outweigh bleed risks (4, 45, 51). The VTE RAMs also suggest, depending on what cut-off is used, that approximately 10–25% of this population is at high risk of VTE (4, 45, 51). Thus we are likely overt-prophylaxing as much as 25% of high VTE risk medical patients, likely by giving an insufficient appropriate duration of thromboprophylaxis, especially in the post-hospital discharge period (52). The use of these validated VTE RAMs in clinical practice has the potential to greatly increase the use of appropriate thromboprophylaxis, including type and duration of pharmacologic thromboprophylaxis, in hospitalised medical patients.

The converse of a VTE RAM in medically ill patients is a scoring tool to identify those patients at high bleed risk, thus minimising inappropriate use of pharmacologic thromboprophylaxis which would place patients at elevated bleed risk. To date there has only been one evidence-derived bleed RAM in this population, using the same derivation methods and scoring system as its VTE counterpart: the IMPROVE Bleed RAM (53). The IMPROVE Bleed RAM used 13 clinical and laboratory factors and designated a score of 7 or more to identify a patient cohort (~10% of the population) at high risk of bleeding (major bleed risk 4.1% vs 0.4%) (Table 3) (53). This Bleed RAM was later externally validated in a cohort of more than 12,000 patients, with good discrimination characteristics (54). Thus both validated VTE as well as bleed risk scores (Padua and IMPROVE VTE and IMPROVE Bleed RAMs) can be used during admission to determine an individual medical patient’s risk of VTE and major bleeding, allowing for a tailored (patient-centric) approach to thromboprophylaxis at the bedside. This can be done using a web-based application (IMPROVE Risk Calculator http://www.outcomes.org/improve) or as an app (Apple App Store) (Figure 1). Medical patients with a Padua VTE score of 4 or more or an IMPROVE VTE score of 2 or more, provided that inappropriate use of pharmacologic thromboprophylaxis

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**Table 1: Risk factors for VTE in hospitalised medical patients – the Padua VTE RAM * [adapted from Ref (45)].**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced mobility</td>
<td>3</td>
</tr>
<tr>
<td>Active cancer</td>
<td>3</td>
</tr>
<tr>
<td>Prior venous thromboembolism (excludes superficial thrombophlebitis)</td>
<td>3</td>
</tr>
<tr>
<td>Already known thrombophilic condition</td>
<td>3</td>
</tr>
<tr>
<td>Recent (&lt;1 month) trauma and/or surgery</td>
<td>2</td>
</tr>
<tr>
<td>Elderly age (&gt;70 years)</td>
<td>1</td>
</tr>
<tr>
<td>Heart and/or respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Acute myocardial infarction or ischaemic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Ongoing hormonal treatment</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>1</td>
</tr>
<tr>
<td>Acute infection and/or rheumatologic disorder</td>
<td>1</td>
</tr>
</tbody>
</table>

* A score of 4 or more constitutes at VTE risk.

**Table 2: Risk score points assigned to each independent VTE risk factor in hospitalised acutely ill medical patients – the IMPROVE VTE associative RAM * [adapted from ref (4)].**

<table>
<thead>
<tr>
<th>VTE risk factor</th>
<th>Points for the risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Thrombophilia**</td>
<td>2</td>
</tr>
<tr>
<td>Lower limb paralysis</td>
<td>2</td>
</tr>
<tr>
<td>Cancer***</td>
<td>2</td>
</tr>
<tr>
<td>Immobilisation****</td>
<td>1</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>1</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; CCU, coronary care unit. * A score of 0–1 constitutes low VTE risk. A score of 2–3 constitutes moderate VTE risk. A score of 4 or more constitutes high VTE risk. ** A congenital or acquired condition leading to an excess risk of thrombosis. *** May include active cancer (excluding non-melanoma skin cancer) or a history of cancer within 5 years. **** Strict definition is complete immobilization confined to bed or chair ≥7 days; modified definition is complete immobilization ≥1 day.

**Table 3: Bleeding risk score points assigned to each independent factor – the IMPROVE Bleed Score* [adapted from ref (53)].**

<table>
<thead>
<tr>
<th>Bleeding risk factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure GFR 30–59 vs ≥60 ml/min/m²</td>
<td>1</td>
</tr>
<tr>
<td>Male vs female</td>
<td>1</td>
</tr>
<tr>
<td>Age 40–80 vs &lt;40 years</td>
<td>1.5</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>2</td>
</tr>
<tr>
<td>CV catheter</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU</td>
<td>2.5</td>
</tr>
<tr>
<td>Renal failure GFR &lt;30 vs ≥60 ml/min/m²</td>
<td>2.5</td>
</tr>
<tr>
<td>Hepatic failure (INR &gt;1.5)</td>
<td>2.5</td>
</tr>
<tr>
<td>Age ≥85 vs &lt;40 years</td>
<td>3.5</td>
</tr>
<tr>
<td>Platelets &lt;50 × 10³ cells/l</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding in 3 months before admission</td>
<td>4</td>
</tr>
<tr>
<td>Active gastroduodenal ulcer</td>
<td>4.5</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; CCU, critical care unit; CV, central venous; GFR, glomerular filtration rate; INR, international normalised ratio. * A score of 7 or more constitutes high bleed risk.
they have an IMPROVE Bleed Risk score of < 7, would be at VTE risk and would warrant pharmacologic prophylaxis during their hospital stay (▶Figure 2). Those with an IMPROVE Bleed Risk score of 7 or more should likely receive mechanical means of prophylaxis.

Recently, based on best available evidence, the IMPROVE VTE RAM in medical patients was given a formal endorsement as part of a call-to-action for global VTE risk assessment by the Steering Committee of the International Society of Thrombosis and Haemostasis for World Thrombosis Day (55). In addition in 2010, the NHS in England, and effective January 1, 2017, the Center for Medicare and Medicaid Services in the US, has mandated the use of standardized VTE RAMs, which include the UK NHS Tool, Padua VTE RAM, and IMPROVE VTE RAMs to individualise VTE risk assessment in order to guide thromboprophylaxis use across hospital systems (56, 57).

**Individualised (patient-level) post-hospital discharge and extended thromboprophylaxis for medically ill patients using risk assessment models and D-dimer as a biomarker**

The most recent 9th Edition ACCP Antithrombotic Clinical Practice Guideline recommendations for medically ill patients suggested against extending the duration of thromboprophylaxis beyond the period of acute hospital stay (44). This was largely due to insufficient net clinical benefit from a strategy of extended
thromboprophylaxis from randomised trials in unselected medically ill patients as previously discussed. However, recent work in the use of a biomarker and clinical RAMs suggest that they may be useful in selecting a high VTE risk cohort of medically ill patients that would likely benefit from extended thromboprophylaxis in the post-hospital discharge period.

The D-dimer (Dd) antigen is a unique marker of fibrin degradation and has clinical utility as an indicator of coagulation activity in a patient (58). Although it has been used in the past as a diagnostic tool to rule out VTE and as a prognostic tool to identify a low risk cohort of patients for VTE recurrence, recent data established the use of an elevated Dd as a biomarker in hospitalised medical patients at risk for VTE (59). A post-hoc analysis from the large MAGELLAN trial in medically ill revealed that an elevated Dd using a cut-off of > 2X the upper limit of normal (ULN) was able to identify a high VTE risk cohort – especially in the post-hospital discharge period – and that this cohort did not incur an increased risk of bleeding, thus predicting net clinical benefit (59).

The good discrimination characteristics of an elevated Dd as a risk model (an area under the ROC curve of approximately 0.70) also suggests that it could be used alone or in combination with a clinical model (59). Lastly, an elevated Dd was able to predict VTE risk in the intermediate period (~35 days) in patients hospitalised with CHF (60). The initial, randomized trial evidence of using an elevated Dd as a biomarker to identify a high VTE risk cohort in medically ill patients was shown in the APEX trial, where the primary efficacy outcome was conducted first in the cohort patient group that was prospectively enrolled using a Dd ≥ 2X ULN with local lab criteria (37). Extended thromboprophylaxis with betrixaban was associated with a 19 % relative risk reduction in the primary efficacy outcome, from 8.5 % to 6.9 %, compared to prophylaxis for 10 days with enoxaparin (p=0.054). As part of a key secondary endpoint, exploratory analysis revealed a statistically significant reduction in symptomatic VTE in the overall population with betrixaban (1.5 % vs 0.9 %, 95% CI 0.42–0.98, p = 0.04), suggesting a net clinical benefit using this outcome (37). Even though this cohort narrowly failed to meet the a priori statistical criterion, further analyses using centralised Dd testing as well as the modified intention-to-treat analysis consistently showed a higher VTE risk cohort than the overall population that benefitted from extended betrixaban, with an approximate 20 % RR in the primary efficacy outcome (37). The elevated Dd cohort did not have an excess of major bleeding events in the betrixaban 80mg versus enoxaparin arms (0.49 % vs 0.66 %, respectively).

Table 4: The IMPROVEDD VTE risk score* [adapted from ref (61)].

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>2</td>
</tr>
<tr>
<td>Current lower-limb paralysis</td>
<td>2</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2</td>
</tr>
<tr>
<td>Immobilised ≥ 7 days</td>
<td>1</td>
</tr>
<tr>
<td>ICU or CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>1</td>
</tr>
<tr>
<td>D-dimer ≥ 2 × ULN</td>
<td>2</td>
</tr>
</tbody>
</table>

* A score of 2 or more constitutes at-VTE risk.
An IMPROVE VTE score of 4 or more is able to identify a high VTE risk medically ill cohort with a symptomatic VTE event rate of 4.74% in the original derivation study and a VTE event rate of 4.15% (95% CI: 2.79–8.12) in a subsequent large external validation study (4, 47). This high risk population likely constitutes about 5–10% of the hospitalised medically ill population (4, 47). A further refinement of the IMPROVE score includes the addition of elevated Dd with 2 points to the original score (the so-called IMPROVE-DD VTE score, ▶Table 4), which may improve model discrimination by approximately 6% (61). Further external validation studies are needed before this model is widely adapted.

Additional evidence for the value of a formal VTE risk assessment combined with measurement of Dd will come from the ongoing large global randomized placebo-controlled trial of extended thromboprophylaxis in medically ill – the MARINER trial, which is randomizing patients to either rivaroxaban or placebo at hospital discharge (62). The study is utilising a modified IMPROVE VTE score (including a broader definition of immobility and the inclusion of a history of cancer only) with a cut-off of 4 or more to identify high VTE risk patients using clinical criteria alone, and an IMPROVE VTE score of 2 or 3 and Dd > 2X ULN to identify a high risk subgroup from an overall moderate VTE risk group (62). The trial is including only symptomatic VTE events (including fatal PE or where fatal PE cannot be ruled out) as the primary efficacy outcome, in accordance with the approach taken by recent guidelines for assessing risk-benefit.

If the results of the MARINER trial produce a net clinical benefit in hospitalised medical patients (and the trial has reasonable power to detect a reduction in VTE-related mortality), then a new paradigm of formalised VTE risk assessment at hospital discharge will be seen as shown in ▶Figure 2. Patients at hospital discharge with an IMPROVE VTE score of 4 or more, or an IMPROVE VTE score of 2 or 3 with elevated Dd (2X ULN) during their hospitalisation, should have an extended 45 day course of thromboprophylaxis with rivaroxaban. It is interesting to note that these criteria mirror remarkably well the final inclusion criteria for the APEX trial using extended betrixaban as well. In addition, depending upon further validation efforts of the IMPROVEDDD VTE score as well as regulatory acceptance of the APEX trial results, one may consider an elevated IMPROVEDDD score or age > 75 years, as secondary VTE risk assessment criteria at discharge as well. Until studies in extended thromboprophylaxis are completed, it would be prudent to offer the minimum duration of thromboprophylaxis – as established by previous trials of 6 to 14 days – in medical patient groups with these high risk features, specifically with an IMPROVE VTE score of 4 or more. Further analysis of local laboratory Dd cut-offs and types of quantitative assays used based on data from APEX and MARINER – when complete – as well as educational efforts surrounding novel use of elevated Dd as a biomarker (not a diagnostic tool) will need to be undertaken before routine use of Dd is performed in clinical practice to identify high VTE risk medical patients.

Conclusions

A recent editorial discussed the limitations of a group-specific VTE risk assessment strategy as applied to previous thromboprophylaxis efforts of heterogeneous medically ill patients (63). The 9th Edition ACCP Guidelines for the first time introduced in 2012 the concept of using a RAM to individualise a medical patient’s thrombotic and bleed risk, thus providing a tailored strategy to maximise benefit-to-risk for thromboprophylaxis in this generally fragile population with multiple co-morbidities and poor cardio-pulmonary reserve. We have also seen in parallel that the shortening hospital length-of-stay seen both in the US and other countries has dampened the treatment effects of in-hospital thromboprophylaxis. In the ensuing years we now have large-scale external validation studies that have established both the Padua VTE and IMPROVE VTE RAM, as well as the IMPROVE Bleed RAM, as robust scored risk models in this population. Lastly, for the first time, a key biomarker to identify medical patients at high VTE risk who would likely benefit from extended thromboprophylaxis, – an elevated Dd (≥ 2X ULN) – has gone through proof-of-concept with results from the APEX trial and will likely undergo further validation when the results of the MARINER trial are published. Depending upon what threshold score is used, a patient can be considered at-risk, or even high risk, for thrombosis or bleeding, necessitating an individualised strategy focusing on type but also optimal duration of thromboprophylaxis both during a patient’s hospital admission and likely at discharge. As these risk assessment tools are now available for large-scale use in a web application or as an app, the era of a personalised approach to the risk of thrombosis and bleeding for an individual hospitalised medical patient, at the bedside, is upon us. Further work in defining a subset of patients with chronic medical illness along with disease severity that may benefit from long-term primary thromboprophylaxis should also be considered. Also, as the VTE RAMs have shown excellent negative predictive value but less ability to show positive predictive value, further research work needs to be done to determine optimal model calibration and cut-offs. Ultimately, international antithrombotic guidelines will need to adopt and endorse these approaches to gain widespread acceptance, but a new paradigm of VTE prevention in medically-ill patients has already begun.

Author contributions

Both authors had full access to all data and contributed to drafting of the paper.

Conflicts of interest

Alex C. Spyropoulos has served as a consultant for Boehringer Ingelheim, Janssen, Bayer Healthcare, and Daiichi Sankyo, and has served on advisory committees for Bristol-Myers Squibb, Pfizer, Janssen, Portola, and Bayer Healthcare; Gary E. Raskob has served as a consultant for Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Janssen, Johnson and Johnson, Merck,
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