



Venous thromboembolism prophylaxis in hospitalized elderly patients: Time to consider a ‘MUST’ strategy

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Abstract

Venous thromboembolism (VTE) is the commonest cause of preventable death in hospitalized patients. Elderly patients have higher risk of VTE because of the high prevalence of predisposing co-morbidities and acute illnesses. Clinical diagnosis of VTE in the elderly patient is particularly difficult and, as such, adequate VTE prophylaxis is of pivotal importance in reducing the mortality and morbidities of VTE. Omission of VTE prophylaxis is, however, very common despite continuous education. A simple way to overcome this problem is to implement universal VTE prophylaxis for all hospitalized elderly patients instead of selective prophylaxis for some patients only according to individual's risk of VTE. Although pharmacological VTE prophylaxis is effective for most patients, a high prevalence of renal impairment and drug interactions in the hospitalized elderly patients suggests that a multimodality approach may be more appropriate. Mechanical VTE prophylaxis, including calf and thigh compression devices and/or an inferior vena cava filter, are often underutilized in hospitalized elderly patients who are at high-risk of bleeding and VTE. Because pneumatic compression devices and thigh length stockings are virtually risk free, mechanical VTE prophylaxis may allow early or immediate implementation of VTE prophylaxis for all hospitalized elderly patients, regardless of their bleeding and VTE risk. Although the cost-effectiveness of this Multimodality Universal STat (‘MUST’) VTE prophylaxis approach for hospitalized elderly patients remains uncertain, this strategy appears to offer some advantages over the traditional ‘selective and single-modal’ VTE prophylaxis approach, which often becomes ‘hit or miss’ or not implemented promptly in many hospitalized elderly patients. A large clustered randomized controlled trial is, however, needed to assess whether early, multimodality, universal VTE prophylaxis can improve important clinical outcomes of hospitalized elderly patients.

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1 Significance of venous thromboembolism

Venous thromboembolism (VTE) is a global public health problem and is the commonest cause of preventable hospital death in many developed countries.^[1,2] The latest data showed that VTE affects over 900 000 patients and causes over 100 000 to 300 000 deaths in the USA each year.^[2,3] The total burden of VTE in the European Union countries was estimated to exceed 1.6 million events, comprising 0.7 million cases of deep vein thrombosis (DVT), 0.4 million cases of non-fatal pulmonary embolism (PE), and 0.5 million VTE-related deaths.^[4] The total cost

of VTE per person including lost of well-being was over US\$1.4 million and the total cost of VTE for Australia in the year of 2008 was about 3.9 billion, more than the costs of all other acute and chronic diseases including cancers.^[5]

The incidence of VTE in elderly patients is very high. The risk of developing VTE exceeds 0.6% per year for the general population who are older than 80 years old (Figure 1).^[6] The risk of VTE is particularly high among hospitalized elderly patients because of the associated risk factors (Figure 2). Many of these acute and chronic risk factors interact with each other and are responsible for the dramatic increase in the overall risk of VTE in hospitalized elderly patients.

Clinical diagnosis of VTE in elderly hospitalized patients is difficult. Elderly patients are much less likely to present with typical symptoms of DVT, such as lower limb discomfort or difficulty in ambulation,^[7,8] but more likely to present with non-specific symptoms often leading to an incorrect diagnosis before PE occurs.^[9-11] Furthermore, biomarkers for early diagnosis of VTE such as D-dimers

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may have different normal values for different age groups and they may not be reliable for patients who have a high pre-test probability of VTE.^[12,13] Indeed, the majority of estimated VTE-related deaths were sudden fatal PE (34%) or undiagnosed VTE (59%); only 7% deaths occurred in those on preventive therapy.^[4] These data suggest that whilst VTE is very common, it is often clinically silent and presents diagnostic difficulties in the majority of hospitalized patients. As such, VTE prophylaxis is of pivotal importance in reducing mortality and morbidity of VTE.

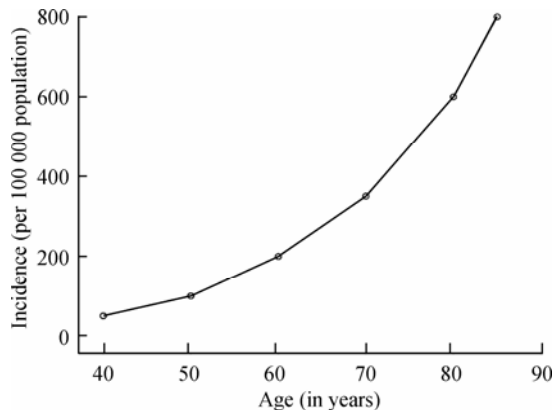


Figure 1. Age-specific incidence of venous thromboembolism in the general population.

Although utilization of VTE prophylaxis in many situations has improved with education, recent studies showed that more than 40% of hospitalized patients who were at risk of VTE were not receiving pharmacological VTE prophylaxis.^[14,15] These results suggest that the current strategy to improve implementation of VTE prophylaxis by continuous education is insufficient. A more effective VTE prophylaxis policy could potentially reduce VTE deaths by more than 0.5 million per year in the USA and European Union countries alone.

2 Limitations of the existing VTE prophylaxis strategy for elderly hospitalized patients

Although major advances in prevention, diagnosis and treatment of VTE have been made in the last two decades, significant problems remain in translating the evidence and guidelines of VTE prophylaxis into clinicians' daily clinical practice. Having more and more efficacious VTE prophylactic agents does not appear to improve or guarantee the effectiveness of VTE prophylaxis implementation for most hospitalized elderly patients. Data from USA showed that only 41% of all elderly patients diagnosed with DVT had received VTE prophylaxis.^[8] In the following section, we

will discuss some limitations of the existing VTE prophylaxis strategy for hospitalized elderly patients.

2.1 Selective VTE prophylaxis

A recently developed risk assessment model suggested that elderly age (> 70 years) is only associated with a slight increase in risk of VTE in hospitalized patients and elderly age alone is not considered as a high-risk factor for developing VTE in hospitalized patients.^[16] Nevertheless, many risk factors for VTE including immobilization (25%), malignancy (10%), congestive heart failure (22%), chronic obstructive airway disease (11%), and diabetes mellitus (16%) are highly prevalent among hospitalized elderly patients (Figure 2).^[6] Furthermore, many elderly patients are admitted to hospital with an acute precipitating cause for VTE, including hip fracture, surgery, cerebrovascular accident or acute myocardial infarction. According to the risk assessment model developed by Barbar *et al.*^[16], any elderly (> 70 years) patients would be considered as having a high-risk of developing VTE if they have one or more of the following factors: immobilization, active cancer, previous VTE, or thrombophilic condition; or if they have three or more of the following factors: obesity (body-mass-index ≥ 30), hormonal therapy, active infection, rheumatologic disorder, acute myocardial infarction, ischaemic stroke, cardiac failure, or respiratory failure; or if they have recent surgery or trauma plus any one of the above mentioned risk factors.

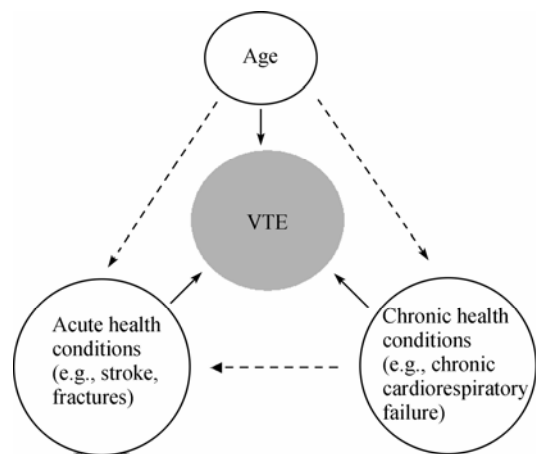


Figure 2. Risk factors for venous thromboembolism (VTE) in hospitalized elderly patients.

A risk assessment model is, in general, a very good tool for stratifying risks of patients when the majority of them are having a relatively low risk, so that a small proportion of patients who have a high risk for the outcome of interest can be selected for further investigation, prophylaxis or treatment. When a risk stratification model is applied to a

cohort of patients who have a high prevalence of the risk factors contained in the model, it becomes an inefficient tool because many patients would be considered to have at least moderate risk. A reliable risk stratification model is also intrinsically complicated, not necessarily generalizable to different patient cohorts, and also needs to be updated regularly.^[17] Using a complicated VTE risk stratification model will certainly complicate the treatment pathways of all hospitalized patients and may reduce the nurses and physicians' compliance with the implementation of VTE prophylaxis.

2.2 Delay in implementing VTE prophylaxis

Both the National Quality Forum and Joint Commission International recommend auditing the proportion of patients who receive VTE prophylaxis or have documentation about why no thromboprophylaxis is given within 24 h of admission as a performance indicator.^[2,18] Observational studies suggest that a delay of more than one to three days in initiating thromboprophylaxis is associated with a significant increase in risk of VTE in patients with major trauma.^[19,20] It is possible that these findings may, at least in part, be generalizable to most hospitalized elderly patients.

There are possibly two reasons why VTE prophylaxis is often delayed or omitted in hospitalized elderly patients. First, the use of a selective approach that recommends different types and levels of VTE prophylaxis for patients with different diagnoses or undergoing different procedures. Although many new initiatives, such as multi-screen set of electronic alerts,^[21-23] have been successfully used in some hospitals to improve implementation of VTE prophylaxis for different patients depending on their individual VTE risk profiles, these initiatives do require a significant amount of resources and may not be possible in many hospitals.

Second, many clinicians perceive the risk of bleeding due to pharmacological antithrombotic agents as more important than the risk of VTE, leading to a delay or even omission of VTE prophylaxis in many patients.^[19,24-26] This concern is, to some extent, justifiable for hospitalized elderly patients. For patients who are older than 80 years old, the risk of major and fatal bleeding is estimated to be 3.4% and 0.8%, respectively. For patients who are older than 90 years old, the risk of fatal bleeding is as high as 13%,^[27-29] especially if they are admitted for severe trauma, hemorrhagic stroke, subdural hematoma, neurosurgery and active gastrointestinal bleeding.^[30,31] Regardless of the causes for a delay in initiating VTE prophylaxis, a delay may turn into omission of VTE prophylaxis altogether during the entire hospital stay of a patient and increases the risk of VTE.^[19,20]

2.3 Effectiveness and bleeding risk of pharmacological VTE prophylaxis

Much of the VTE prophylaxis research has been focusing on superiority or equivalence of different pharmacological agents. Pharmacological VTE prophylaxis is recommended as the main mode of VTE prophylaxis for most hospitalized patients by the latest American College of Chest Physicians' guidelines and there is no doubt that it will remain the most important method to prevent VTE.^[32] Elderly patients have, however, a much higher risk of bleeding after receiving pharmacological VTE prophylaxis than younger patients, partly due to frequent occurrences of renal impairment and drug interactions.^[33] Evidence suggests that bleeding from antithrombotic agents is a strong predictor of mortality and will reduce the overall benefits of VTE prophylaxis in hospitalized patients.^[28,34] As such, we have to interpret the benefit to risk ratio of many pharmacological VTE prophylactic agents when applied to hospitalized elderly patients with caution.

Although low molecular weight heparin (LMWH) and fondaparinux are more efficacious than unfractionated heparin (UFH) in some situations (e.g., hip and knee joint arthroplasty, major trauma, ischemic stroke),^[35] the concerns about an increased risk of bleeding with LMWH among hospitalized elderly patients persist among many clinicians. According to the data from RIETE prospective registry in Europe, LMWH remained as an independent risk factor for bleeding for elderly patients.^[28] This may be because renal impairment and drug interactions are by far more common in a real world clinical setting than in patients recruited in a commercial VTE prophylaxis trial. For example, in the ARTEMIS trial of fondaparinux on older hospitalized medical patients (> 60 years old), patients who were at a high risk for bleeding or had recent hemorrhagic or ischemic stroke, neurological or ophthalmological surgery, and renal impairment (serum creatinine level > 180 $\mu\text{mol L}^{-1}$ in a well hydrated patient) were all excluded.^[36] Similarly, in the MEDENOX trial of enoxaparin on acutely ill medical patients, despite excluding patients who were at risk of increased bleeding (renal impairment: serum creatinine > 150 $\mu\text{mol L}^{-1}$, uncontrolled arterial hypertension, active peptic ulcer, coagulopathy, or other conditions that could increase the risk of hemorrhage), fatal hemorrhage still occurred in 0.3% and 0.6% of the patients who received daily 20mg and 40mg enoxaparin, respectively.^[37]

Evidence suggests that UFH 5000 units t.d.s. is as effective as LMWH in hospitalized medical patients.^[38] In the PREVAIL Trial of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after

acute ischaemic stroke,^[39] daily enoxaparin 40 mg was more effective than UFH 5000 units b.d. in reducing a composite end-point of all asymptomatic and symptomatic VTE events (relative risk [RR] = 0.57, 95% confidence interval [CI] = 0.44–0.76), but the rate of extracranial hemorrhage was also higher after enoxaparin (1% *vs.* 0%, *P* = 0.015). Again, patients with renal impairment (creatinine clearance < 30 mL min⁻¹), severe liver disease or coagulopathy were all excluded in this study. Although heparin induced thrombocytopenia related to UFH remains as a concern (LMWH *vs.* UFH, RR = 0.29, 95%CI = 0.06–1.42, *P* = 0.13),^[40] its shorter duration of action and reversibility with protamine relative to LMWH, anti-Xa or anti-thrombin agents for make it more preferable for VTE prophylaxis when the bleeding risk is high or when the patient has renal impairment.^[33] The major risk factors for bleeding from VTE prophylaxis are described in Table 1.^[29]

Table 1. Major risk factors for bleeding.^[29]

Active gastroduodenal ulcer
Bleeding episodes within three months prior to admission
Platelet count < 50 × 10 ⁹ cells/L
Elderly age (> 85 years old)
Elevated International Normalized Ratio (INR) 1.5
Renal impairment with estimated creatinine clearance < 30 mL/min/m ²
Admitted to the intensive care or coronary care unit

3 Time to consider a ‘MUST’ approach to VTE prophylaxis for hospitalized elderly patients

We propose a Multimodality Universal STat (‘MUST’) approach to overcome the problem of frequent delays or omissions of VTE prophylaxis for many hospitalized elderly patients. Although the ‘MUST’ approach consists of three elements, they are intrinsically interrelated and should be interpreted as a single strategy that aims to improve the utilization of VTE prophylaxis for hospitalized elderly patients in a pragmatic fashion.

First, in order to overcome the concerns about bleeding from pharmacological prophylaxis and, at the same time, avoid a delay in initiating VTE prophylaxis for hospitalized elderly patients, mechanical VTE prophylaxis has an important role to play within the first 24–72 h of hospitalization of elderly patients. Although the overall benefits and risks of these devices, such as lower limb pneumatic compression devices, thigh length stockings and inferior vena cava (IVC) filters, for many hospitalized patients remain controversial,^[41,42] their role may be particularly important for hospitalized elderly patients than young patients

due to the much high risk of bleeding of the elderly patients with pharmacological VTE prophylaxis. Limited evidence suggests that non-invasive mechanical VTE prophylaxis such as lower limb pneumatic compression devices and thigh length stockings, alone may be quite effective in reducing VTE in high-risk patients.^[43–46] Furthermore, some evidence suggests that combining mechanical VTE prophylaxis with UFH can be more effective than UFH alone.^[47] Recent evidence also suggests that early mobilization has been underutilized and is indeed safe and important in preventing complications of VTE in hospitalized patients.^[48–50] Although large randomized controlled trials comparing LMWH against UFH (either a t.d.s or b.d. regimen) with mechanical VTE prophylaxis and early mobilization are still lacking, a multimodality approach by combining low-dose UFH and compression devices and early mobilization for hospitalized elderly patients appears logical and maybe superior to LMWH alone, especially if the patients have significant risk factors for bleeding.

For a minority of elderly patients who have physical injuries to their lower limbs preventing non-invasive mechanical VTE prophylaxis and also at high-risk of bleeding, a retrievable inferior vena cava filter may represent the only option of VTE prophylaxis until the bleeding risk improves. Therefore, a multimodality VTE prophylaxis approach, by combining low-dose UFH, mechanical prophylaxis (compression devices and thigh length stockings) and early mobilization, may represent the most pragmatic approach so that most, if not all, hospitalized elderly patients can receive VTE within 24 h of hospitalization.

Second, because many risk factors for VTE are so prevalent among elderly hospitalized patients,^[8] we can argue that risk stratification by a complicated scoring system is, in fact, not necessary, and may only complicate the treatment pathway or reduce the compliance to VTE prophylaxis. One possible way to improve implementation of VTE prophylaxis for all hospitalized elderly patients is to treat every single hospitalized elderly patient (e.g., > 70 years old) as having a high-risk for VTE, as they should be, and automatically receive VTE prophylaxis without requiring other risk factors for VTE. A universal VTE prophylaxis, similar to universal precautions for infectious risks associated with blood and body fluids, so that VTE prophylaxis has to be opted out instead of opted in stands the best chance to change the practice or behaviours of clinicians on VTE prophylaxis and, if successful, may reduce over 50% of VTE complications in hospitalized patients.^[51]

Third, starting VTE prophylaxis immediately (STat or

statim) upon hospitalization for all elderly patients (Universal) will not be possible unless the risks associated with such prophylaxis are very low for all patients. Because non-invasive mechanical VTE prophylaxis, such as thigh length stockings and pneumatic compression devices on the lower limbs, are virtually free of bleeding risk and do not require a physician's prescription, these VTE prophylaxis measures can be initiated immediately by ward nurses as soon as an elderly patient is hospitalized. Apart from offering some degree of immediate protection against VTE, the presence of a mechanical VTE prophylaxis device itself, or when it is also labelled with a VTE prophylaxis reminder, may serve very well to remind the attending physician the need to initiate pharmacological VTE prophylaxis (e.g., low dose UFH) when they see the patients. Using non-invasive mechanical VTE prophylaxis as a reminder for physicians to initiate pharmacological VTE prophylaxis may be easier than using complicated multi multi-screen set of electronic alerts.

In summary, despite significant advances in VTE prophylaxis that have been achieved in the last two decades, an unmet gap between evidence and practice exists and many suitable hospitalized elderly patients remain untreated with VTE prophylaxis. Perhaps, it is time for us to consider a different approach to improve the implementation of VTE prophylaxis for hospitalized elderly patients. Non-invasive mechanical VTE prophylaxis and early mobilization should be implemented for all elderly patients as soon as they are hospitalized. An 'opt out' stands a better chance than an 'opt in' system for implementation of VTE prophylaxis. The components of the multimodality approach, as discussed in the review, should remain dynamic and be adjusted when the VTE and bleeding risk of a patient changes during the course of hospitalization and after hospital discharge. A large clustered randomized controlled trial is, however, needed to assess whether early, multimodality, universal VTE prophylaxis will improve important clinical outcomes of hospitalized elderly patients.

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