Routine pharmacological venous thromboembolism prophylaxis in frail older hospitalised patients: where is the evidence?

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Abstract

It has been claimed that there are over 25,000 preventable in-hospital deaths from venous thromboembolism annually in the UK. NICE and SIGN guidelines therefore recommend that all hospitalised patients are risk assessed for venous thromboembolism. The guidelines would recommend using pharmacological thromboprophylaxis for all patients aged 60 and above with reduced mobility and acute medical illness unless obvious contra-indications exist. Meta-analysis data regarding pharmacological thromboprophylaxis for medical patients demonstrate reductions in asymptomatic deep vein thrombosis (DVT) rather than fatal pulmonary embolism and mortality. There is also the potential for increased bleeding risk with this approach. Evidence for older medical in-patients, particularly those aged over 75, is more limited being derived from subgroup analyses of larger clinical trials. In addition, based on exclusion criteria such as increased bleeding risk, frailr older adults were unlikely to have been included within such trials. This commentary will (i) critically appraise available data on the incidence of DVT and PE in older hospitalised patients; (ii) review the evidence available from meta-analyses and subgroup analyses in older medical in-patients for the use of venous thromboembolism prophylaxis; (iii) discuss those situations out-with the guidelines where venous thromboprophylaxis may not be appropriate and even potentially harmful in this patient group and (iv) suggest future research directions.

Keywords: venous thromboembolism, deep vein thrombosis, pulmonary embolism, prophylaxis, older people, elderly

Introduction

NICE and SIGN guidelines recommend that all hospitalised patients are assessed for the risk of venous thromboembolism (VTE) [1, 2]. Essentially, any adult ≥60 years with reduced mobility and acute medical illness should receive pharmacological thromboprophylaxis unless contra-indications exist [1, 2]. Notably, the latter apply regardless of age. The Royal College of Physicians, the Academy of Medical Royal Colleges, the Royal College of Nursing and the Royal Pharmaceutical Society have jointly endorsed the NICE guidance [3].

Such bold recommendation does not sit well with the ethos of clinical geriatrics where one tailors management to the individual patient and circumstances in a holistic manner. As hospitals face penalties over non-compliance with policies and guidelines, geriatricians’ ability to deliver such patient-centred care is under threat [4, 5].

Search strategy

Electronic databases (Medline, PubMed, Embase and Cochrane Library) were searched from their inception until November 2012, identifying studies looking at: (i) the incidence and risk of VTE within hospitalised medical patients aged over 75 and (ii) the evidence from randomised placebo-controlled trials of pharmacological thromboprophylaxis in hospitalised medical patients aged over 75 years. Relevant keywords included venous thromboembolism,
deep vein thrombosis, pulmonary embolism (PE), prevention/prophylaxis and elderly/aged. The searches were restricted to English language, peer-reviewed journal articles. Reference lists from relevant articles were scrutinised for further trials and the evidence supporting key publications from NICE, SIGN, Department of Health and House of Commons Health Committee were reviewed.

Randomised controlled trials which included either a significant proportion of older patients (i.e. >50% aged ≥75) or that reported a subgroup analysis of the aged ≥75 population were selected for inclusion. Where a trial did not explicitly state the proportion of participants aged ≥75, or where the trial’s exclusion criteria included those aged over 80, then these were excluded from this paper. One study by Dahan et al. [6] specifically recruited patients aged ≥65 years, but was excluded as the administered 60 mg dose of enoxaparin is greater than standard prophylactic doses. Any trial involving patients with only a single disease such as stroke or myocardial infarction, those comparing unfractionated and low molecular weight heparin head-to-head, or those studies focusing on VTE in community rather than hospital settings were excluded. Consequently, we think that our summary of the evidence is unlikely to be prone to selection bias.

VTE risk: are the figures right?

A House of Commons Health Committee report in 2005 stated that in-hospital VTE accounts for >25,000 preventable deaths [1, 7]. Subsequently, the Department of Health reported a figure of >60,000 preventable VTE deaths annually within the UK population [8]. This latter figure results from epidemiological modelling, where data on VTE incidence within hospital and community settings are combined with an algorithm linking the likelihood of undiagnosed deep vein thrombosis (DVT) progressing to fatal PE [9].

Some concerns arise from these reports. First, it is assumed that thromboprophylaxis will prevent these deaths [7, 8]. Secondly, the Health Committee report offers no primary reference for the figure of >25,000 preventable deaths. Instead, evidence from an American study within that report suggests a PE incidence of 23 per 100,000 with deaths. Instead, evidence from an American study within the Health Committee report estimates 60,000 cases of in-hospital VTE annually [7]. However, a mortality rate exceeding >40% would be required to fit with figures claiming >25,000 preventable deaths.

Recent post-mortem data suggest much lower mortality rates from in-hospital PE at 2% [11]. With 284,000 hospital deaths in 2007 for England and Wales then 5,680 could be attributed to PE, which again is considerably less than the claimed >25,000 figure [11].

In comparison, recent annual mortality figures for England and Wales report 500,000 deaths, with 3,000 certified due to PE [12]. If deaths from venous disease are included, the figure is still <7,000 [12].

Does advancing age increase VTE risk in medical in-patients?

Alikhan et al. [13] reported increased VTE risk in patients >75 years (RR: 1.51, 95% CI: 1.03–2.20). This risk was derived from retrospective analysis of the MEDENOX trial population and might not be applicable to unselected frail older adults who may have fulfilled the exclusion criteria (Table 1) [13, 14]. Additionally, only three cases of PE occurred with placebo in this trial so the risk predominantly relates to asymptomatic DVT.

Spyropoulos et al. [15] reported a higher VTE incidence within 3 months of hospitalisation in patients >60 years versus those ≤60 years (HR: 2.0, 95% CI: 1.3–2.9). However, the difference between patients >75 years versus those ≤75 years was not significant (HR: 1.2, 95% CI: 0.8–1.6).

The evidence for an age-associated increase in the risk of in-hospital PE is inconsistent. One retrospective study of 210 PE cases reported an incidence of 0.6% in patients aged 15–49, 1.5% in those aged 50–69 and 1.4% in patients ≥70 years [16]. Although the incidence in those ≥50 years was significantly higher (P < 0.05) versus the 15–49 cohort, there was no further increase in incidence with age beyond 70. In contrast, Kniffin et al. [17] reported an increased PE incidence beyond 70 years, i.e. 1.3/1,000 in those aged 65–69 versus 2.8/1,000 in those ≥85 years (RR: 2.29, 95% CI: 2.09–2.51). However, these figures were obtained using Medicare hospital discharge claims and relied upon retrospective analysis of discharge coding, thus curtailing data interpretation.

Is pharmacological thromboprophylaxis beneficial?

General population

Meta-analyses show reduced DVT risk with pharmacological thromboprophylaxis. However, this mainly involves asymptomatic events with at best an absolute risk reduction (ARR) of 3%, and no significant reduction in symptomatic DVT [18–22]. For any PE, the ARR was 0.3–0.75% [20, 21–24]. Dentali et al. [20] reported an ARR in fatal PE of 0.25% but this meta-analysis included two unblinded trials. No other meta-analysis reports a reduction in fatal PE [20]. The incidence of PE from meta-analyses, even with placebo, was 1%, with fatal PE less frequent at 0.4% [20, 23].

Notably, the risks of any bleeding event are increased by 2% [22, 24]. For major bleeding, the increased absolute risk is 0.15–0.5%, although not always significant [18–23].
<table>
<thead>
<tr>
<th>Trial</th>
<th>MEDENOX</th>
<th>PREVENT</th>
<th>ARTEMIS</th>
</tr>
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<tbody>
<tr>
<td><strong>Pharmacological agent compared with placebo</strong></td>
<td><strong>Enoxaparin 40 or 20 mg</strong></td>
<td><strong>Dalteparin 5000 IU</strong></td>
<td><strong>Fondaparinux 2.5 mg</strong></td>
</tr>
<tr>
<td><strong>Total number of patients</strong></td>
<td>1,102</td>
<td>3,706</td>
<td>849</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>≥40</td>
<td>≥40</td>
<td>≥60 (age range 53–96)</td>
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<td><strong>Female (%)</strong></td>
<td>50</td>
<td>51.9</td>
<td>57.6</td>
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<td><strong>Patients &gt;75 years (%)</strong></td>
<td>50.3</td>
<td>33.3</td>
<td>51.7</td>
</tr>
<tr>
<td><strong>Primary composite endpoint</strong></td>
<td>Venographic distal or proximal DVT, symptomatic DVT or PE or fatal PE from Day 6 to 14</td>
<td>Ultrasonographic proximal DVT, symptomatic DVT or PE, fatal PE or sudden death by Day 21</td>
<td>Venographic distal or proximal DVT, symptomatic DVT or PE, fatal PE by Day 15</td>
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<tr>
<td><strong>Patients included with the following medical conditions and/or risk factors</strong></td>
<td>Either acute respiratory failure or cardiac failure (NYHA III or IV) or an acute medical condition plus 1 additional risk factor</td>
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<td>Any of the following:</td>
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<tr>
<td><strong>Acute medical conditions:</strong></td>
<td>Infection</td>
<td>Infection</td>
<td></td>
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<td></td>
<td>Acute rheumatological disorders</td>
<td>Acute rheumatological disorders</td>
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<td></td>
<td>Inflammatory bowel disease</td>
<td>Inflammatory bowel disease</td>
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<td><strong>Additional risk factors:</strong></td>
<td>Age ≥75, cancer, previous VTE, obesity, varicose veins, hormone replacement therapy (not post-menopausal HRT), chronic cardiac or respiratory failure</td>
<td>Age ≥75, cancer, previous VTE, obesity, varicose veins, chronic venous insufficiency, HRT, history of chronic respiratory or cardiac failure or myeloproliferative disorder</td>
<td></td>
</tr>
<tr>
<td><strong>Reasons for exclusion from the trial relevant to frail older hospitalised adults</strong></td>
<td>Inability to provide informed consent</td>
<td>Inability to provide informed consent</td>
<td>Inability to provide informed consent</td>
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<td></td>
<td>Recent immobility &gt;3 days</td>
<td>Recent immobility &gt;3 days</td>
<td>High risk for bleeding</td>
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<td></td>
<td>Serum creatinine &gt;150 µmol/l</td>
<td>Serum creatinine &gt;177 µmol/l</td>
<td>Serum creatinine &gt;180 µmol/l</td>
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<td></td>
<td>Major surgery within last 3 months</td>
<td>Major surgery or invasive procedure in the last month or due within 2 weeks</td>
<td>Major surgery or invasive procedure in the last month or due within 2 weeks</td>
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<td></td>
<td>Septic shock</td>
<td>Septic shock</td>
<td>Septic shock</td>
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<td></td>
<td>Hypertension (BP ≥200 mmHg systolic and/or diastolic ≥120 mmHg)</td>
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<td></td>
<td>Bacterial endocarditis</td>
<td>Bacterial endocarditis</td>
<td>Bacterial endocarditis</td>
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<td></td>
<td>Active peptic ulcer</td>
<td>Active peptic ulcer</td>
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<td></td>
<td>Known thrombophilia</td>
<td>Known thrombophilia</td>
<td>Known thrombophilia</td>
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<td></td>
<td>On anticoagulant therapy</td>
<td>On anticoagulant therapy</td>
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<td></td>
<td>Platelet count &lt;100 × 10^9/l</td>
<td>Platelet count &lt;100 × 10^9/l</td>
<td>Platelet count &lt;100 × 10^9/l</td>
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<td>Clotting disorder (prolonged-activated partial-thromboplastin time, prothrombin ratio &lt;50%, INR &gt;1.2)</td>
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<td>Clotting disorder (prolonged-activated partial-thromboplastin time, prothrombin ratio &lt;50%, INR &gt;1.2)</td>
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<tr>
<td><strong>Trial outcomes (total population):</strong></td>
<td>Enoxaparin 40 mg versus Placebo</td>
<td>Dalteparin 5000 IU versus Placebo</td>
<td>Fondaparinux 2.5 mg versus Placebo</td>
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<td><strong>Primary endpoint</strong></td>
<td>16/291 (5.5%) versus 43/288 (14.9%)</td>
<td>42/1,518 (2.77%) versus 73/1,473 (4.96%)</td>
<td>18/321 (5.6%) versus 34/323 (10.5%)</td>
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<td><strong>RR:</strong></td>
<td>0.37 (95% CI: 0.21–0.64)</td>
<td>0.55 (95% CI: 0.38–0.80)</td>
<td>0.54 (95% CI: 0.31–0.92)</td>
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</table>
Overall, there is no significant reduction in all-cause mortality [18–24]. Lederle et al. [22] concluded that for every 1,000 patients given pharmacological thromboprophylaxis, three PEs were prevented at a cost of nine bleeding events, four of which would be major bleeding, with no mortality benefit.

Finally, the LIFENOX trial, referenced in the joint Colleges’ endorsement of the NICE guideline, showed no significant mortality reduction with enoxaparin and graduated compression stockings (GCS) versus placebo, either during the 14-day study period, 2.9 versus 2.9% (RR: 1.0, 95% CI: 0.8–1.3) or at 90 days, 8.4 versus 8.6% (RR: 1.0, 95% CI: 0.8–1.1) [25]. Similarly, there was no significant mortality reduction from PE or sudden death, either at Day 14, 0.5 versus 0.7% (RR: 0.7, 95% CI: 0.4–1.3) or Day 90, 1.1 versus 1.0% (RR: 1.1, 95% CI: 0.7–1.6) [25].

**Older patients**

The MEDENOX trial, with half of participants ≥75 years, demonstrated an ARR of 9.4% for the composite endpoint of any DVT or PE with 40 mg enoxaparin versus placebo (Table 1) [14]. Notably, two-thirds of VTE events prevented were asymptomatic, i.e. venographically detected distal DVT. Symptomatic DVT only accounted for 6% of cases and with placebo, only three non-fatal PE occurred. An increase of 3.3% for minor bleeding and 0.6% for major bleeding occurred, although significance values were not reported. A subgroup analysis in those aged ≥75 demonstrated an ARR of 14.4% for VTE, but no bleeding outcome data were provided [26].

The PREVENT trial, with one-third of participants ≥75 years, demonstrated an ARR of 2.2% with dalteparin versus placebo for the composite endpoint, with approximately two-thirds of cases ultrasonographically detected DVT (Table 1) [27]. In those ≥75 years, an ARR of 3.8% for VTE was reported, with a 0.4% increase in major bleeding, albeit non-significant [28].

The ARTEMIS trial, with half of participants ≥75 years, demonstrated an ARR of 4.9% for fondaparinux in VTE reduction (Table 1) [29]. All cases were asymptomatic, venographically detected DVT barring five cases labelled as fatal PE with placebo. However, three of the fatal PE were diagnosed without a post-mortem. A 1.6% increase in minor bleeding occurred with fondaparinux. Unlike MEDENOX and PREVENT, there is no published subgroup analysis for those ≥75.

These trials report significant treatment effects for composite outcomes relying on reducing asymptomatic DVTs over symptomatic or fatal PE. From a clinical standpoint, the importance of detecting asymptomatic DVT is questionable and it is unclear how many patients subsequently develop significant events. Perhaps more importantly, frail older adults are unlikely to have participated within such trials based on exclusion criteria such as increased bleeding risk (Table 1) [14, 27, 29]. Therefore, although older
in-patients may be at a greater risk of VTE, the risk–benefit ratio of pharmacological thromboprophylaxis in unselected frailter patients is unknown.

Pooling of the published data from MEDENOX, PREVENT and ARTEMIS trials (random effects meta-analysis undertaken using the metan command in STATA v10; StataCorp LP, College Station, TX, USA) demonstrates a statistically significant reduction in the composite endpoint (which were broadly comparable across all three trials) for ‘all ages’ and for those aged ≥75 (Figure 1) [14, 26–29]. The risk of major bleeding is increased twofold for both groups, and all-cause mortality was 20% higher in those aged ≥75; although the pooled data lacked confirmatory statistical power (Figure 1). Owing to the limitations of the published data, those aged ≥75 in our forest plot are being compared with ‘all ages’. A further limitation is that only limited ‘age ≥75’ data have been published for MEDENOX and no ‘age ≥75’ data are available for ARTEMIS.

Further areas of uncertainty

Although general contra-indications to pharmacological thromboprophylaxis apply regardless of age, there are additional issues in frailter, older adults:

(i) Bleeding risk is a concern and for that reason, patients with moderate-severe renal impairment or liver dysfunction were excluded from trials [14, 27, 29]. Safety data suggest patients with low bodyweight, a marker for frailty, have greater bleeding risks with enoxaparin despite dose reduction [30]. Furthermore, daily injections are more likely to cause haematoma in this group [4, 30].

Figure 1. Pharmacological thromboprophylaxis in hospitalised general medical in-patients and older adult subgroup aged ≥75 years [14, 26–29].
(ii) Cognitive impairment, an important exclusion criterion in trials, compromises capacity to consent. Co-existent agitation may make administering injections difficult.

(iii) Determining prior mobility, in the presence of cognitive impairment and/or delirium, might be challenging particularly if no corroborative history is available. Perhaps more importantly, the evidence to warrant pharmacological prophylaxis in patients chronically immobile is lacking, and those immobile for >3 days before hospitalisation were excluded from trials (Table 1) [14, 27, 31].

Moreover, changing practice with early comprehensive geriatric assessment and resultant shorter hospital stays may lessen VTE risk for older patients. Conversely, for those remaining hospitalised beyond the trials’ study period (typically 6–21 days), it is unclear whether continuing pharmacological thromboprophylaxis is associated with favourable outcomes.

Finally, some patients are nearing the end of life and, the priority being palliation, thromboprophylaxis may be inappropriate or even harmful [4]. A difficulty here is correctly identifying those patients with <1 month to live which was another trial exclusion [27, 29].

**Conclusion**

Although national guidelines recommend pharmacological thromboprophylaxis for all older medical in-patients unless contra-indicated, the suggested benefit of reducing clinically important VTE and saving lives, together with an acceptable risk of bleeding events, is not strongly supported by the available evidence. It is unclear how the original figures for in-hospital VTE preventable deaths were generated, whether there is a substantial and clinically relevant increase in VTE/PE risk with advancing age in older medical in-patients, and whether pharmacological thromboprophylaxis leads to a meaningful reduced risk of symptomatic DVT and PE events. Of particular note is the limited representation of geriatric medicine specialists in the development of such guidelines.

Moreover, uncertainty exists around the risk of harm from bleeding, particularly in frail patients with multiple co-morbidities as they were excluded from participating in clinical trials. Pending further evidence, we believe that geriatricians are justified in avoiding routine pharmacological thromboprophylaxis for older medical in-patients, particularly in the frailer group.

Where do we go from here? Identifying the true incidence of clinically relevant VTE in a naturalistic setting would help define the magnitude of the problem. If pharmacological thromboprophylaxis is still considered beneficial, further clinical trials should include patients with various degrees of co-morbidity, frailty and duration of exposure. Only then could the true efficacy and safety of this approach be determined in our patients.

**Key points**

- NICE and SIGN guidelines recommend VTE risk assessment for all hospitalised patients.
- Accordingly, hospitalised adults ≥60 years with reduced mobility and acute medical illness should be given pharmacological thromboprophylaxis unless obvious contra-indications exist.
- Meta-analysis evidence suggests that pharmacological thromboprophylaxis predominantly reduces asymptomatic deep vein thrombosis rather than fatal PE or mortality.
- Frail, older adults were more likely to be excluded from clinical trials due to exclusion criteria such as increased bleeding risk.
- Although limited evidence suggests hospitalised older adults may be at a greater risk of VTE, the risk–benefit ratio of pharmacological thromboprophylaxis is unknown, particularly in the frailer group.

**Conflicts of interest**

None declared.

**Supplementary data**

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

**References**

The very long list of references supporting this commentary has meant that only the most important are listed here and are represented in bold type throughout the text. The full list of references is given in Supplementary data (Appendix 1) available in *Age and Ageing* online.


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