Rational thromboprophylaxis in medical inpatients: not quite there yet

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ABSTRACT

- Routine thromboprophylaxis in hospitalised medical patients is based on trials that predominantly use asymptomatic deep vein thrombosis (DVT) as the endpoint.
- As asymptomatic DVT is 10–30-fold more common than symptomatic DVT, this exaggerates estimates of benefit and cost-effectiveness.
- Based on symptomatic disease, the number needed to treat per venous thromboembolism (VTE) prevented is high (150–1600), and the true cost-effectiveness of thromboprophylaxis for symptomatic event reduction is uncertain.
- The incidence of major bleeding among patients receiving prophylaxis is at least equal to the reduction in clinical VTE.
- Routine thromboprophylaxis in hospitalised medical patients is not warranted, and better patient selection is needed.

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Development of a system to ensure appropriate prophylaxis of deep vein thrombosis (DVT), venous thromboembolism (VTE) and pulmonary embolism (PE) in hospital patients is now widely advocated,[1] and guidelines are available in Australia[2,3] and overseas.[4,5] However, despite substantial literature showing the effectiveness of thromboprophylaxis, the evidence base for clinical decision making in individual patients remains controversial, especially in medical patients. There is uncertainty over the benefits, patient selection, cost-effectiveness and total cost. Current Australian guidelines concentrate on prophylaxis for surgical patients.

Role of prophylaxis

Asymptomatic DVT can be detected by venography in 10%–17% of general medical patients who are bedbound for 2 or more days, while symptomatic DVT and PE (including fatal PE) occur in 0.5%–1% of such patients.[6-8]

Prophylaxis of disease aims to prevent conditions with significant symptoms or risk of death; resources spent on preventing trivial or asymptomatic disease are wasted. The American College of Chest Physicians (ACCP) guidelines assert that the main reason for thromboprophylaxis is prevention of PE, which is potentially fatal.[4] The importance of other sequelae (eg, post-thrombotic syndrome) in medical patients is uncertain, as there are no data on the benefit of prophylaxis; these sequelae are not included as factors to be considered in any guidelines.

The commonly advocated forms of thromboprophylaxis are low molecular weight heparin (LMWH) and unfractionated heparin (UH). LMWH has been shown to be more effective than UH.[9] Enoxaparin is the only LMWH registered for prophylaxis for medical patients in Australia.

All trials to date have assessed the effect of LMWH prophylaxis using techniques that detect asymptomatic disease (eg, venography).[6-8] Using asymptomatic endpoints produces a high value of absolute risk reduction with prophylaxis that is of questionable clinical relevance. Further, economic models containing this artificially high absolute benefit are biased in favour of prophylaxis.

Evidence base for thromboprophylaxis

Trial data

Level 1 evidence would be obtained from a randomised, placebo-controlled trial of enoxaparin or equivalent, powered to reveal an effect on symptomatic DVT or PE. No such trials exist, possibly because the infrequency of symptomatic events would necessitate very large sample sizes (about 20 000 patients for a one-sided test with $\alpha = 0.05$ and a power of 90%).

Closest to this ideal is the PREVENT (Prevention of Recurrent Venous Thromboembolism) study, a randomised, placebo-controlled trial of 3706 medical patients that measured the effect of dalteparin (a LMWH) 5000 IU/day on a composite primary endpoint of symptomatic DVT and PE plus asymptomatic DVT events measured after 21 days of treatment.[8] Unlike related studies,[6,7] the PREVENT trial was not unduly affected by treatment given to patients found to have an asymptomatic DVT. When compared with placebo, dalteparin reduced the incidence of symptomatic proximal DVT (0.11% v 0.40%) and PE (0.28% v 0.34%). The low event numbers precluded statistical analysis, but the trial-based estimate of the number needed to treat (NNT) to prevent each PE, symptomatic proximal or any symptomatic DVT were 1666, 344 and 285, respectively.[8]

Similar relative reductions in asymptomatic DVT diagnosed by venography were found for the higher of two doses of enoxaparin (40 mg) compared with placebo (MEDENOX [Prophylaxis in Medical Patients with Enoxaparin]; $n = 1102$)[7] and of fondaparinux (ARTEMIS [Arixtra for Thromboembolism Prevention in a Medical Indications Study]; $n = 849$).[6] In MEDENOX, very few patients had symptomatic or fatal PE (40 mg dose group, 0; placebo group, 2) or symptomatic DVT (40 mg, 1; placebo, 2).[7] In ARTEMIS, zero (active treatment) and five (placebo) patients had PE after 15 days; no symptomatic DVT was observed in either group at 15 or 30 days.[6] These results could have been affected by the use of venography, but overall, the data show that symptomatic DVT or PE is very uncommon in medical patients.

Prevention of symptomatic events occurring after the relatively short periods of trial follow-up may reduce the NNT. In another trial, an additional 23% of medical patients developed a clinical VTE event within 90 days after discharge, with a plateau thereafter.[10] In the PREVENT study, the corresponding finding was 37%. However, these high percentages arise from low absolute baseline rates, and do not substantially affect the proposition that the absolute risk reduction of symptomatic events with prophylaxis is small.

Mortality was higher in the treated group in the PREVENT trial,[8] and no significant difference was found in the ARTEMIS[6] or MEDENOX[7] studies. No difference in mortality was found in a randomised prospective study of nadroparin prophylaxis compared with placebo, powered to detect a 3% reduction in mortality.[11] Trends in the opposite direction have also been detected.[7,12] Thus, the effect of prophylaxis on mortality is unresolved.

1 Rates of major bleeding with low molecular weight heparin (LMWH) thromboprophylaxis or placebo

	Major bleeding		Total bleeding	
Study	LMWH	Placebo	LMWH	Placebo
ARTEMIS[6]*	0.20%	0.20%	2.60%	1.00%
MEDENOX[7]†	1.70%	1.10%	12.50%	8.60%
PREVENT[8]‡	0.49%	0.16%	1.52%	0.71%

* Fondaparinux 2.5 mg/day. † Enoxaparin 20 or 40 mg/day; data for 40 mg/day only. ‡ Dalteparin 5000 IU/day. ◆

Meta-analyses

Two meta-analyses have found significant effects of thromboprophylaxis on VTE, at low absolute rates.[9,13] One excluded small studies ($n<30$) and studies in stroke patients,[13] while the other included stroke trials, small studies and studies in summary form (letter or abstract).[9] Both found that LMWH thromboprophylaxis reduced symptoms of VTE,[9,13] but the NNT was again high (DVT, 232; PE, 345; fatal PE, 400).[13] One review included several studies of doubtful relevance: one used a 60 mg dose of enoxaparin, another was performed in an intensive care setting, a third was a pilot study, and others focused on survival benefit only or involved UH.[13] Thus, although statistical tests of heterogeneity were negative, the actual heterogeneity of the studies is striking. In the other meta-analysis, the NNT to prevent one PE was 185. Five of the 11 studies examined ischaemic stroke; others included an abstract, a letter, and a trial of anticoagulant treatment of stroke.[9] Several trials showed no benefit. In spite of these possible disadvantages, the meta-analyses confirm that the absolute rates of symptomatic VTE, and the benefit of prophylaxis, are low in medical patients.

Bleeding risks

Box 1 shows bleeding rates in the three main trials of LMWH. The major bleeding risk reported by one meta-analysis was 0.58% with enoxaparin and 0.44% with placebo.[13] However, another meta-analysis reported a significantly higher risk of major, minor and total bleeding and injection site haematoma.[9] In PREVENT, major bleeding was nearly twice as frequent as PE (0.28%).[8] Thus, the risk of major bleeding with prophylaxis is of at least the same magnitude as the reduction in VTE. This is an argument against prophylaxis in the PREVENT study patient population.

Alternative forms of prophylaxis

Alternative drugs and mechanical devices are available for thromboprophylaxis, and may be efficacious and cost-effective. Aspirin has been shown to be as effective as UH,[14] but the net effect of co-administration of aspirin and anticoagulants on thrombosis and bleeding is uncertain and needs to be further investigated.

New thromboprophylaxis drugs are under development, and may be trialled in medical patients. Among these are the oral direct thrombin inhibitors apixaban and dabigatran. The antithrombotic effect of these is similar to that of enoxaparin in surgical patients,[15,16] so their impact, if any, may depend on their adverse effect profiles and cost.

Compression stockings are well established as effective in preventing VTE after surgery, at a cost equivalent to 5 days' treatment with LMWH. However, with only one trial in medical patients, there is insufficient evidence to advocate their widespread use.[17]

Cost-effectiveness

Published economic analyses compare LMWH with UH,[18-22] or are derived from the MEDENOX trial.[20-21,23] The former provide only a relative cost-effectiveness, in which LMWH dominates by reducing bleeding and heparin-induced thrombocytopenia.[18-21] The latter, by including reduced asymptomatic events as "benefits", inflate cost-effectiveness and lack clinical relevance. Hence, the cost-effectiveness of thromboprophylaxis cannot be assumed.

At the current cost of enoxaparin ($4.20/day for 40 mg) and using trial-based data, the drug acquisition cost per event prevented is about $20 000–$94 000. This measure is incomplete, as it excludes the cost of excess bleeding and savings from reduced symptomatic VTE rates, although these factors tend to cancel each other out. The available data do not currently support inclusion of a mortality benefit or quality-of-life adjustment. According to current guidelines, thromboprophylaxis for medical patients may not satisfy the usual cost-effectiveness criteria.

Who should receive thromboprophylaxis?

The ACCP guidelines[4] recommend thromboprophylaxis for patients represented in trials such as MEDENOX[7] and PREVENT.[8] The authors of these studies correctly acknowledge that most trial data relate to asymptomatic endpoints and suggest (reasonably) that the relative risk reduction is similar for symptomatic endpoints. However, the profound implications arising from the use of asymptomatic endpoints, and from the low symptomatic event rates, are not discussed. Further, the general implications of the increased risk of bleeding with prophylaxis are not discussed. Claims of cost-effectiveness cite MEDENOX data, so they are only valid if prevention of asymptomatic events is considered an economic benefit. Other international guidelines recommend more restricted prophylaxis, such as in patients who are acutely ill and bedbound with a history of VTE, malignant disease, or who are aged over 75 years.[5] These guidelines seem more likely to select appropriate patients.

On the basis of the data presented here, and in contrast with Australian[2] and international[4,5] guidelines, rational thromboprophylaxis requires further patient selection, based on clinical trial populations and risk factor analysis. Risk factors for VTE in medical patients have been documented in several studies.[24-27] Relative risk is higher in patients with previous DVT or VTE, those with a malignancy, and in pregnant women (relative risk [RR], 2.06–15.6, 1.62–6.53, and 11.41, respectively) but relatively low in others, including patients with chronic obstructive pulmonary disease (RR, 1.33), congestive heart failure (RR, 1.36–1.72), or most notably, those aged over 75 years (RR, 1.03).[24-27] Age greater than 60 years is a primary selection criterion for prophylaxis in current Australian guidelines.[2,3]

Because the risk factors span a wide range of relative risk, devising a set of decision-making criteria is not a straightforward task. A simple approach might be to restrict prophylaxis to the PREVENT study clinical population (Box 2) but with a requirement for two or more risk factors, except perhaps in patients with cancer or previous DVT. The validity of such an approach needs to be assessed in detail. Further, patients with ischaemic stroke were excluded from the major trials,[6-8] so their inclusion in current guidelines[2] is controversial.

Routine thromboprophylaxis in medical patients is not justified on the basis of low clinical need, high NNT, uncertain cost-effectiveness and poor benefit–hazard ratio. Further restriction to selected patients at highest risk will improve overall clinical and economic benefit, and should be the basis of more explicit national guidelines for medical patients.

2 PREVENT study population[8]

Inclusion criteria: Patients were considered for inclusion if they:

- were ⩾ 40 years old;
- had an acute medical condition requiring a projected hospitalisation of ⩾ 4 days;
- had ⩽ 3 days of prior immobilisation; and
- had one of the following disease-based risk factors:
  - ➢ acute congestive heart failure;
  - ➢ acute respiratory failure not requiring ventilatory support;
  - ➢ infection without septic shock;
  - ➢ acute rheumatological disorders; or
  - ➢ inflammatory bowel disease.
- Patients with any of the last three inclusion criteria required at least one additional risk factor: age ⩾ 75 years; cancer; previous VTE; obesity; varicose veins and/or venous insufficiency; hormone replacement therapy; history of chronic heart failure; chronic respiratory failure; or myeloproliferative disorder.

Exclusion criteria were: acute coronary syndrome in the past month; major surgical or invasive procedure in the past month or due within 2 weeks; bacterial endocarditis; immobilised lower limb because of a cast or fracture; stroke within the past 3 months; high risk of bleeding; platelet count $< 100 \times 10^9$/L; thromboprophylaxis for > 48 hours before randomisation; hepatic insufficiency or active hepatitis; pregnancy or breastfeeding; or life expectancy < 1 month.

PREVENT = Prevention of Recurrent Venous Thromboembolism.
VTE = venous thromboembolism. ◆

Competing interests

None identified.

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