Thromboembolic events can be avoided by appropriate risk-assessment and thromboprophylaxis

Abstract

Venous thromboembolism (VTE) is a common event in hospitalised patients and a significant cause of preventable hospital-related patient mortality, being responsible for 10 times the number of deaths per annum than are attributable to methicillin resistant *Staphylococcus aureus* infection. Although VTE is mostly considered to be associated with recent surgery or trauma, the majority of cases occur in non-surgical patients, particularly those with one or more known risk factors, such as advanced age, obesity, immobility or paresis, heart failure or stroke. Evidence from clinical trials supports the use of pharmacological thromboprophylaxis with heparin, including low molecular weight heparin and unfractionated heparin, to reduce the rate of VTE in intermediate and high risk patients. Recent guidelines from NICE and the Department of Health recommend the risk assessment of all hospitalised patients for the consideration of thromboprophylaxis measures.

Introduction

It is estimated that venous thromboembolism (VTE) causes more than 25,000 potentially preventable deaths per year in England.[1,2] This figure includes both patients admitted for medical care and those admitted for surgery, and is five times higher than the number of people who die as a result of hospital acquired infection,[1] and 10 times higher than mortality caused by methicillin resistant *Staphylococcus aureus* (*MRSA*).[2] Without thromboprophylaxis the incidence of objectively confirmed hospital acquired deep vein thrombosis (DVT) is approximately 10–40% among medical or surgical patients and 40–60% following major orthopaedic surgery.[3] Pulmonary embolism accounts for one in 10 deaths in medical patients.[3]

In March 2005, the Health Select Committee report[4] highlighted the importance of thromboprophylaxis in medical patients. The efficacy and safety of thromboprophylaxis has been clearly demonstrated in randomised clinical trials for both medical and surgical patients.[5,6,7,8] However, thromboprophylaxis is poorly implemented in the UK.[2] This may be due to a lack of awareness of the condition and its causes by health care professionals, since the majority of VTE occurs after discharge from hospital.[2] There has also historically been a lack of national guidance on the use of thromboprophylaxis for both medical and surgical patients.

The recent publication of the NICE guidance for surgical inpatients[9] and the Department of Health Independent Expert Working Group report (*The prevention of VTE in hospitalised patients*)[1] aim to address these issues.

Risk factors for venous thromboembolism

The risk of VTE associated with surgical patients is well recognised. The degree of risk is dependent upon factors inherent in the operation, such as the type and duration of the surgical procedure,[10] with major surgery, particularly orthopaedic including hip or knee arthroplasty, conferring an increased risk,[3] and factors related to the individual patient, such as female gender, advanced age and obesity.[3]

Risk factors for VTE in hospitalised, non-surgical patients include the presence of certain conditions, such as heart failure or cancer, and the possession of certain characteristics, such as advanced age and obesity, as indicated in Table 1. Most hospital in-patients will have one or more of these.[1,3,11]

Surgical thromboprophylaxis

The Chief Medical Officer (CMO) recently published the independent expert working group report on prevention of VTE in hospitalised patients.[1] Soon after, the NICE

Table 1. Risk factors for venous thromboembolism in hospitalised patients[1,3,11]

Conditions	Clinical Characteristics
Acute infectious disease[1]	Previous VTE[3]
Congestive cardiac failure[11]	Older age[3]
Acute myocardial infarction[11]	Recent surgery/trauma[3]
Acute respiratory disease[1]	Immobility or paresis[3]
Stroke[11]	Obesity[3,11]
Inflammatory bowel disease[3,11]	Central venous catheterisation[3]
Cancer[11]	Inherited/acquired thrombophilia[3]
	Varicose veins[3,11]
	Oestrogen therapy[3]

Table 2. Summary of recommendations for surgical thromboprophylaxis from the VTE independent experts working group[1]

All hospitalised patients:
Mandatory risk assessment for VTE and consideration of thromboprophylactic measures

High risk surgical/ orthopaedic patients:
Should be managed according to the NICE guidance

Intermediate risk surgical patients (or those with concomitant medical conditions):
Graduated compression stockings combined with heparins (UFH or LMWH)

Low risk surgical patients:
No specific thromboprophylaxis
Early mobilisation on account of the duration or nature of the surgical procedure

Key: UFH = unfractionated heparin; LMWH = low molecular weight heparin

guidance on thromboprophylaxis in surgical patients was released.[9]

Both NICE and the VTE experts group stress the importance of a documented mandatory risk assessment of every hospitalised patient on admission.[1,9] Before surgery all patients should receive information on the risks of VTE and the effectiveness of mechanical and pharmacological prophylaxis.[1,9] This will need to be firmly embedded in the trusts' risk management framework: 100% compliance with risk assessment will be a key performance measure.[1] The recommendations of the VTE experts group for surgical thromboprophylaxis are shown in Table 2.[1] A summary of the NICE recommendations are shown in Table 3.[9]

It is generally agreed that high risk surgical patients (orthopaedic surgery or surgery with additional risk factors for VTE) should receive pharmacological thromboprophylaxis, with low molecular weight heparin (LMWH) or unfractionated heparin (UFH).[1,9] In addition, all hip fracture patients and those hip replacement patients who have patient-related risk factors will require extended prophylaxis for four weeks after their surgery.[9]

There is, however, on-going discussion about the relative merits of mechanical thromboprophylaxis (such as, graduated compression stockings) and pharmacological thromboprophylaxis in the intermediate to low risk patient population. It is worth noting that most of the available evidence for a reduction in VTE risk concerns pharmacological thromboprophylaxis.

Neither guideline recommends the use of aspirin for VTE prevention in any patient group.[1,9]

Table 3. Summary of recommendations for thromboprophylaxis from NICE guidelines for VTE[9]

Surgical speciality (excludes day case surgery)	No patient-related risk factors	One or more patient-related risk factors
Elective hip replacement	Mechanical + LWMH/Fond	Mechanical + LWMH/Fond continued for 4 weeks
Hip fracture	Mechanical + LWMH/Fond continued for 4 weeks	Mechanical + LWMH/Fond continued for 4 weeks
Other orthopaedic	Mechanical + LWMH/Fond	Mechanical + LWMH/Fond
General	Mechanical	Mechanical + LWMH/Fond
Gynaecological	Mechanical	Mechanical + LWMH
Cardiac	Mechanical	Mechanical + LWMH*
Thoracic	Mechanical	Mechanical + LWMH
Urological	Mechanical	Mechanical + LWMH
Neurosurgery	Mechanical	Mechanical + LWMH**
Vascular	Mechanical	Mechanical + LWMH

*Key: Fond = fondaparinux; LMWH = low molecular weight heparin; Mechanical = graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices; * = if not otherwise anticoagulated; ** = except patients with ruptured cranial or spinal vascular malformations if the lesion has not been secured.*

Medical thromboprophylaxis

Although VTE is most often considered to be associated with recent surgery or trauma, 50–70% of symptomatic thromboembolic events occur in non-surgical patients,[3] and hospitalisation for an acute medical illness is independently associated with about an 8-fold increased relative risk for VTE.[3] The recently published NICE guidance only address the use of thromboprophylaxis in surgical patients,[9] although NICE plan to extend their guidance to medical patients in the near future.[12]

The VTE expert group recommends that, as for surgical patients, all medical patients should be risk assessed on admission to hospital.[1] The group will assist with development of a national risk assessment tool although several local models are already available.[13,14,15] Table 4 shows an example of a risk assessment tool for medical thromboprophylaxis.[13]

Three clinical trials have compared the efficacy of the LMWH's enoxaparin (MEDENOX; prophylaxis in MEDical patients with ENOXaparin),[6] dalteparin (PREVENT; Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilised Patients),[7] and fondaparinux (ARTEMIS; ARixtra for

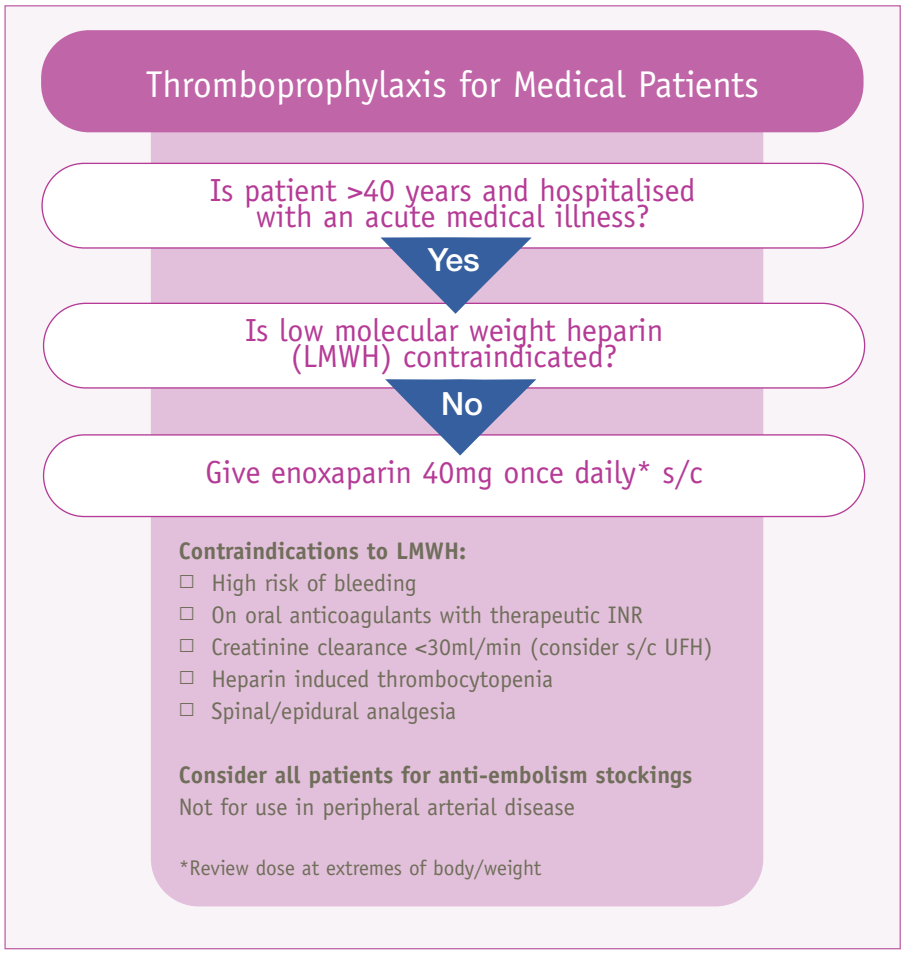

Table 4. Risk assessment criteria for medical patients from Kings College Hospital NHS Trust[13]

ThromboEmbolism Prevention in a Medical Indications Study)[8] with placebo in reducing the risk of VTE in medical patients. Analysis of the primary efficacy endpoints of asymptomatic deep vein thrombosis (DVT), symptomatic VTE or fatal pulmonary embolism (PE) by day 14 (MEDENOX and ARTHEMIX) or day 21 (PREVENT) demonstrated the effectiveness of pharmacological thromboprophylaxis in medical in-patients. However, mechanical methods of thromboprophylaxis used alone have not been appropriately evaluated in acutely ill medical patients and therefore they are not recommended at present.[1]

Studies have shown that patients who are particularly at risk from VTE are those with myocardial infarction, heart failure, chest infection, sepsis and acute stroke with lower limb paralysis.[3,16]

Thromboprophylaxis for the prevention of VTE after stroke is significantly underused.[4,17] DVT and PE are frequent complications of stroke, with a number of studies from different countries finding that 13–25% of early deaths after stroke could be attributed to PE.[17,18] Patients who have an acute ischaemic stroke with lower limb paralysis have about a 50% risk of DVT within two weeks in the absence of heparin prophylaxis.[17] The perceived increase in bleeding risk among stroke patients has meant that pharmacological thromboprophylaxis is generally underprescribed in this patient group.[4,19,20]

Low molecular weight heparin and unfractionated heparin have both been shown to reduce the risk of DVT in stroke patients.[17] Furthermore, data from a meta-analysis suggests that prophylactic low dose LMWH may provide the best benefit to risk ratio in patients with acute ischaemic stroke by decreasing the risk of both DVT (OR=0.34, 95% CI=0.19-0.59) and PE (OR=0.36, 95% CI=0.15-0.87), without increasing the risk of intracranial or extracranial haemorrhage (odds ratio [OR]=1.39, 95% CI=0.53-3.67 and OR=1.44, 95% CI=0.13-16 respectively).[21]

Sherman and co-workers undertook a large-scale multinational, randomised study (the PREVAIL study) to compare the efficacy and safety of the LMWH enoxaparin with that of unfractionated heparin for VTE prophylaxis in patients with acute ischaemic stroke.[22] 1762 patients with acute ischaemic stroke who were unable to walk unassisted received either enoxaparin or unfractionated heparin within 48 hours of the onset of symptoms for 10 days and were assessed for efficacy and safety.

The main findings from this study were that enoxaparin reduced the risk of VTE by 43% compared with unfractionated heparin (68 [10%] vs 121 [18%]; relative risk 0.57, 95% CI 0.44-0.76, p=0.001; difference -7.9%, -11.6 to -4.2) by day 14.[22] The incidence of symptomatic venous thromboembolism did not differ significantly between the enoxaparin and unfractionated heparin groups, and the risk of PE was lower in the enoxaparin group, with one patient who received enoxaparin developing PE compared with six patients who received unfractionated heparin, although this difference was not significant (p=0.059; see Table 5).[22] There was no significant difference in the occurrence of symptomatic intracranial haemorrhage between the two groups, although the incidence of major extracranial haemorrhage was significantly higher in the enoxaparin group (7 [1%] vs 0; p=0.015). This did not, however, lead to increased mortality.[22]

At present the 'gold standard' guidance from The American College of Chest

Table 5. Incidence of venous thromboembolic events up to day 14 in the efficacy group (PREVAIL study)[22]

	Enoxaparin (n=666)	UFH (n=669)	Relative risk (95% CI)	p
VTE	68 (10%)	121 (18%)	0.57 (0.44-0.76)	0.0001
Symptomatic VTE	2 (<1%)	7 (1%)	0.29 (0.06-1.38)	0.096
PE	1 (<1%)	6 (1%)	0.17 (0.02-1.39)	0.059

Key: PE = pulmonary embolism; UFH = unfractionated heparin

Physicians recommends the use of unfractionated heparin or LMWH for acute stroke patients with restricted mobility.[3]

Pharmacists' roles in thromboprophylaxis

The independent experts working group recommends the formation of multi-disciplinary thrombosis teams within all NHS trusts to provide leadership with regard to VTE management and thromboprophylaxis.[1] These committees will agree on the local strategy for prevention of VTE, which will need to take the form of a written thromboprophylaxis policy including risk assessment and the provision of appropriate thromboprophylaxis. The specialist pharmacist is a key member of this team and is instrumental in developing policies, auditing outcomes relating to thromboprophylaxis and ensuring compliance with local guidelines. Pharmacists also play an important role in the education of other health care professionals in the use of thromboprophylaxis. Patient safety is a priority for all NHS trusts and pharmacists are increasingly taking a lead in this area. Thromboprophylaxis initiatives are an important part of increasing patient safety for hospitalised patients.

Conclusion

It is more cost effective to prevent thrombosis than to treat it. The recent publication of the NICE guidance[9] and the VTE experts' report[1] has highlighted the need for robust strategies to implement thromboprophylaxis in all NHS trusts. Pharmacists are well placed to offer appropriate advice and knowledge about the available anticoagulants to ensure that treatment is appropriate and optimal, and to reduce the incidence of anticoagulant therapy related complications. It is likely that they will increasingly be called upon to assist in audit, education and development of evidence-based guidance in this area.

Disclaimer

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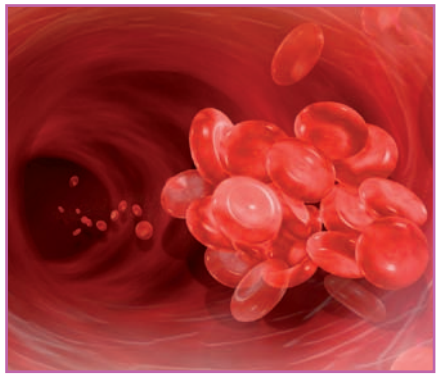
Rosalind Perrott, senior pharmacist, Haematology and Anticoagulation, King's College Hospital, London



References

1. Department of Health. *Report of the Independent Expert Working Group on the prevention of venous thromboembolism (VTE) in hospitalised patients (April 2007)*. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_073944 Last accessed 25 September 2007.
2. Fitzmaurice D, Murray E. Thromboprophylaxis for adults in hospital. *BMJ* 2007; **334:** 1017–8.
3. Geerts WH, Pineo GF, Heit JA *et al*. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and thrombolytic therapy. *Chest* 2004; **126(3 suppl):** 338S–400S.
4. House of Commons Health Committee. *The prevention of venous thromboembolism in hospitalised patients. Second report of session 2004-5*. March 2005. Available at: http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/99/99.pdf Last accessed 1 November 2007.
5. Lassen MR, Davidson BL, Gallus A *et al*. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost* 2007; **5(12):** 2368–75. epub doi: 10.1111/j.1538-7836.2007.02764.x
6. Samama MM, Cohen AT, Darmon JY *et al*. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* 1999; **341(11):** 793–800.
7. Leizorovicz A, Cohen AT, Turpie AGG *et al*. PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004; **110(7):** 874–9.
8. Cohen AT, Davidson BL, Gallus AS *et al*. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 2006; **332:** 325–9.
9. National Institute for Health and Clinical Excellence. Guidance CG46: *Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery*. Full guideline (April 2007). Available at http://guidance.nice.org.uk/CG46 Last accessed 25 September 2007.
10. Agnelli G, Bolis G, Capussotti L *et al*. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery. *Ann Surg* 2006; **243:** 89–95.
11. Leizorovicz A and Mismetti P. Preventing venous thromboembolism in medical patients. *Circulation* 2004; **110:** IV 13–19.
12. National Institute for Health and Clinical Excellence. *Venous Thromboembolism — Prevention: final scope*. October 2007. Available at http://www.nice.org.uk/guidance/index.jsp?action=download&o=37889. Last accessed 8 November 2007.
13. Kings College Hospital NHS Trust. Thromboprophylaxis for medical patients. Risk assessment criteria.
14. Queens Medical Centre, Nottingham, University Hospital NHS Trust. *The prescription of thromboprophylaxis for medical patients*. 2005. Available at: http://www.fons.org/Thrombosis/projects/pdfs/NottinghamReportDec2005.pdf
15. Norfolk and Norwich University Hospital NHS Trust. *Trust guideline for the management of thromboprophylaxis in trauma and orthopaedic patients*. 2006. Available at: http://www.nnuh.nhs.uk/docs%5Ctrustdocs%5C249.pdf
16. Geerts WH, Heit JA, Clagett GP *et al*. Prevention of venous thromboembolism. *Chest* 2001; **119:** 132–75.
17. Kelly J, Rudd A, Lewis R *et al*. Venous thromboembolism after acute stroke. *Stroke* 2001; **32:** 262–7.
18. Kelly J, Hunt BJ, Rudd A, Lewis RR. Pulmonary embolism and pneumonia may be confounded after acute stroke and may co-exist. *Age and ageing* 2002; **31:** 235–9.
19. Zotz RB, Decousus H, Monreal M *et al*. Venous thromboembolism prophylaxis in acutely ill medical patients : do perceived risk factors for bleeding influence physicians practices? Findings from the International Medical Prevention Registry On Venous Thromboembolism (IMPROVE). *J Thromb Haem* 2005; **3(Suppl 1):** Abstract P1099.
20. Waldo AL, Becker RC, Tapson VF *et al*. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol* 2005; **46(9):** 1729–36.
21. Kamphuisen PW, Agnelli G. What is the optimal pharmacological prophylaxis for the prevention of deep vein thrombosis and pulmonary embolism in patients with acute ischaemic stroke? *Thromb Res* 2006; **119:** 265–74.
22. Sherman DG, Albers GW, Bladin C *et al*. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet* 2007; **369:** 1347–55.