Venous thromboembolism: a UK perspective

Venous thromboembolism remains a significant cause of morbidity and mortality in the UK, and its dangers, particularly in hospitalized patients, have long been recognized. Recent measures to tackle this problem and new treatments should alleviate the burden of venous thromboembolism for patients, their families and hospital services.

The Chief Medical Officer, Sir Liam Donaldson, published a risk assessment for venous thromboembolism, recommended for all patients admitted to hospital in England, in September last year (Department of Health, 2008). Venous thromboembolism accounts for more than 25 000 deaths in the UK each year (Health Select Committee, 2005). This is thought to represent more than the combined death toll from breast cancer, acquired immunodeficiency syndrome (AIDS) and road traffic accidents (Health Select Committee, 2005). Venous thromboembolism is often asymptomatic, can be misdiagnosed and therefore is often unrecognized as the cause of death (Cohen et al, 2007).

Venous thromboembolism occurs as a result of inappropriate activation of the body's clotting mechanism resulting in intravascular thrombosis. The most common form of venous thromboembolism is deep vein thrombosis. More seriously, fragments can break away from blood clots in the leg veins and travel to the lungs causing pulmonary embolism. Pulmonary embolism is a potentially fatal condition that can also cause longer term damage to the lungs.

Around 30% of people with venous thromboembolism will go on to develop pulmonary embolism (White, 2003) which accounts for 10% of all hospital deaths (Geerts et al, 2004) and is the most common avoidable cause of death in hospital patients. A quarter of pulmonary embolism patients will die within 7 days and about 30% die within 30 days (Kroegel and Reissig, 2003) of their presentation event. Patients may also develop post-thrombotic syndrome, a painful and potentially disabling condition associated with the development of leg ulcers which are persistent and difficult to heal. Around 4% of patients with pulmonary embolism develop chronic pulmonary hypertension (Pengo et al, 2004), a serious and potentially fatal complication caused by obstruction of the pulmonary blood vessels.

The problem of venous thromboembolism was widely reported in the general media following the Health Select Committee's (2005) report on the prevention of venous thromboembolism in hospitalized patients. In responding, the government recognized the importance of a systematic approach to identify those patients at risk of venous thromboembolism associated with hospital stay. It acknowledged that there was no systematic approach to identifying these patients and that there was significant room for improvement.

In announcing the new national risk assessment for venous thromboembolism, the Chief Medical Officer recognized that the creation of a standardized national strategy was a world first. This welcome step will help to identify those at highest risk for the development of venous thromboembolism and thus prompt initiation of appropriate thromboprophylaxis for those who could benefit most.

Risk factors

A number of risk factors have been identified for venous thromboembolism (Heit, 2002). These include:

- Increasing age
- Male gender
- Recent surgery
- Trauma
- Confinement to hospital or nursing home
- Neurological disease with extremity paresis
- Central venous catheter or transvenous pacemaker
- Previous vein thrombosis
- Varicose veins
- Pregnancy
- Use of oral contraceptives
- Hormone replacement therapy.

The greatest risk attends patients admitted to hospital with serious medical illness, those with cancer, and those undergoing major general or orthopaedic surgery. Guidance from the Department of Health (2008) identifies the following as patient-related factors in a high-risk thrombosis category:

- Age >60 years
- Previous pulmonary embolism or deep vein thrombosis
- Active cancer
- Acute or chronic lung disease
- Acute or chronic inflammatory disease
- Chronic heart failure
- Lower limb paralysis (excluding acute stroke)

Professor Ajay Kakkar *is Professor of Surgical Sciences and Dean for External Relations at Barts and the London School of Medicine and Dentistry Hospital and Director of the Thrombosis Research Institute, London SW3 6LR*

- Acute infectious disease
- Body mass index >30 kg/m^2.

The risk of pulmonary embolism in the absence of prophylaxis is around 5% in the highest risk groups following surgery and around 1% in acutely ill medical patients (National Institute for Health and Clinical Excellence (NICE), 2007). But although venous thromboembolism risk factors have long been documented, in 2004–5 there were around 64 000 finished consultant episodes with a diagnosis of venous thromboembolism.

Prevention

Methods of preventing venous thromboembolism are mechanical or pharmacological. Mechanical methods, such as the use of graduated compression or anti-embolism stockings, or pneumatic calf compression, reduce the incidence of deep vein thrombosis but have yet to demonstrate efficacy in the prevention of pulmonary embolism when used alone. Among the most popular pharmacological methods are low-dose and low molecular weight heparin, fondaparinux and oral anticoagulant drugs such as vitamin K antagonists.

In April 2007 NICE produced guidance for the prevention of venous thromboembolism in patients undergoing orthopaedic and high risk surgery (NICE, 2007). This recommended:

- All surgery patients should be assessed for risk of venous thromboembolism
- The use of compression stockings unless contraindicated
- The use of low molecular weight heparin or fondaparinux in high-risk patients
- Low molecular weight heparin or fondaparinux should be continued for 4 weeks after hip fracture surgery
- Encouraging patients to become mobile as soon as possible.

The Department of Health's new risk assessment strategy and future NICE guidance on the prevention of venous thromboembolism, due for publication in September 2009, has the potential to spearhead a reduction in mortality and morbidity from venous thromboembolism. NICE has commissioned the National Collaborating Centre for Acute Care to develop a clinical guideline on reducing the risk of venous thromboembolism in all hospital patients.

The guidance will cover surgical inpatients, inpatients with acute medical illness, trauma patients, patients admitted to intensive care units and cancer inpatients (NICE, 2007). Mechanical and pharmacological interventions will be considered, along with nursing care and physiotherapy.

Pharmacological thromboprophylaxis

Pharmacological thromboprophylaxis usually involves the use of a subcutaneous anticoagulant such as low molecular weight heparin or fondaparinux. The low molecular weight heparins have been extensively evaluated for the prevention and treatment of venous thromboembolism. New oral anticoagulant drugs are becoming available and have been evaluated for the prevention of venous thromboembolism in high-risk surgical patients.

Advances in anticoagulation

Antithrombotic therapy began when traditional anticoagulants first became available over 60 years ago. The search for new anticoagulants was triggered by the recognition of the clinical limitations of traditional anticoagulants such as heparin and the vitamin K antagonists – the need for monitoring and multiple food and drug interactions. Newer parenteral compounds such as low molecular weight heparin, fondaparinux and other agents were subsequently developed.

The development of selective inhibitors of specific coagulation factors was stimulated by a greater understanding of the biochemistry and molecular biology of blood coagulation, with the objective of creating agents that had the potential to be more effective, safer and easier to use than existing anticoagulants. However, the first modern oral agent to be developed, the direct thrombin inhibitor ximelagatran, was withdrawn from the market in 2006 following concerns about liver toxicity. This was a setback in the search for an improved drug armamentarium for the prevention and treatment of thrombosis but recent developments may have overcome this hurdle. New oral anticoagulants have been developed that directly inhibit either thrombin or factor Xa.

Direct thrombin inhibitors

In September 2008, NICE and the Scottish Medicines Consortium (SMC) recommended the oral anticoagulant dabigatran for the primary prevention of venous thromboembolism in adults undergoing total knee replacement and total hip replacement. Dabigatran etexilate is a direct inhibitor of thrombin, a key enzyme in thrombus formation which enables the conversion of fibrinogen to fibrin during the coagulation cascade. Inhibition of thrombin prevents clot formation. The appraisal committee for NICE assessed phase III trials in elective knee and hip replacement patients comparing dabigatran with the low molecular weight heparin, enoxaparin, given as an injection, for the prevention of venous thromboembolism.

The committee discussed the clinical effectiveness of dabigatran compared with low molecular weight heparin and with fondaparinux (although there was no direct evidence comparing these two agents), as well as the relative acceptability and ease of management conferred by oral as opposed to subcutaneous administration. Comparison with low molecular weight heparin is the key comparator because fondaparinux is used much less extensively (NICE, 2008). The committee con-

cluded that dabigatran was 'likely to be of equivalent clinical and cost effectiveness to LMWH [low molecular weight heparin] or fondaparinux in the prevention of VTE [venous thromboembolism]' and acknowledged that 'oral administration of dabigatran, without the need for monitoring, would reduce administration costs and may support adherence to treatment'. This latter point may influence clinical practice to better prevention of venous thromboembolism. The main concern limiting use of anticoagulant therapy for the prevention of venous thromboembolism is a fear of bleeding which may affect the surgical site and ultimately increase the incidence, or worsen the consequences, of deep infection in the surgical site. Bleeding rates in these trials were similar between these two groups (dabigatran and low molecular weight heparin comparator drugs) (NICE, 2008). Dabigatran is approved for use throughout the European Union by the European Medicines Agency.

Factor X inhibitors

Rivaroxaban

In July 2008, the European Committee for Medicinal Products for Human Use recommended approval of rivaroxaban, an oxazolidinone derivative that inhibits the enzyme factor Xa, a key component of the blood clotting process taken once daily for the prevention of deep vein thrombosis and pulmonary embolism in patients undergoing elective hip or knee replacement surgery. This recommendation was based on a review of the RECORD clinical trial programme. NICE (2009) has recommended rivaroxaban for the prevention of venous thromboembolism as an option in adults having elective total hip replacement surgery or elective total knee replacement.

The RECORD (REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE) programme, involving almost 12 000 patients, is the most extensive evaluation of a novel strategy for prevention of venous thromboembolism in high-risk surgical patients. RECORD-1, published in the *New England Journal of Medicine*, was a randomized, double-blind trial comparing the efficacy and safety of a postoperative dose of rivaroxaban once daily with subcutaneous enoxaparin 40 mg, starting the evening before surgery and administered once daily thereafter, for extended thromboprophylaxis after hip surgery. A superiority analysis showed that rivaroxaban was significantly more effective than enoxaparin in preventing venous thromboembolism events (Eriksson et al, 2008). The two drugs had similar safety profiles. Major bleeding occurred in six out of 2209 patients (0.3%) in the rivaroxaban group and in two of 2224 patients (0.1%) in the enoxaparin group (P=0.18).

The primary efficacy outcome of composite deep vein thrombosis, non-fatal pulmonary embolism or death from any cause at 36 days occurred in 18 of 1595 patients (1.1%) in the rivaroxaban group and in 58 of 1558 patients (3.7%) in the enoxaparin group, a relative risk reduction of 70% in favour of rivaroxaban.

The RECORD-2 study (Kakkar et al, 2008) compared the use of rivaroxaban for extended thromboprophylaxis with short-term thromboprophylaxis using enoxaparin followed by placebo after total hip arthroplasty. It showed that extended thromboprophylaxis was significantly more effective than short-term enoxaparin plus placebo for the prevention of venous thromboembolism, including symptomatic events. RECORD-3 (Lassen et al, 2008) compared rivaroxaban 10 mg once daily with enoxaparin 40 mg per day, each for 10–14 days, in 2531 patients undergoing total knee arthroplasty. It showed that rivaroxaban reduced significantly the incidence of primary and secondary end points compared with enoxaparin, with a similar incidence of bleeding events. RECORD-4 (Turpie et al, 2009) showed that rivaroxaban provided total knee replacement surgery patients with statistically significant reduction of total venous thromboembolism events compared to enoxaparin 30 mg twice daily, the higher North American prophylaxis dose (6.9% *vs* 10.1%, P=0.012). The rate of major bleeding in the rivaroxaban group was similar to the enoxaparin group (0.7% *vs* 0.3% respectively, P=0.11).

The European Commission has given marketing authorization for rivaroxaban in all EU member states. The availability of an oral anticoagulant that is effective and safe in preventing venous thromboembolism in patients undergoing orthopaedic surgery may improve prophylaxis.

Apixaban

Apixaban is another oral factor Xa inhibitor developed for the prevention of venous thromboembolism. The companies that license and market apixaban, BMS and Pfizer, announced in August 2008 that its phase III venous thromboembolism prevention trial, ADVANCE-1 trial, showed that apixaban missed its primary end point in patients undergoing knee surgery, failing to meet statistical criteria for non-inferiority when compared with enoxaparin.

ADVANCE-1 compared apixaban 2.5 mg twice daily to enoxaparin 30 mg twice daily. The primary efficacy outcome was a composite of symptomatic or asymptomatic deep vein thrombosis, pulmonary embolism and death by any cause. The rate of the primary efficacy end point on apixaban was numerically similar to that observed with enoxaparin (9.0% *vs* 8.9%, P=0.064), but did not meet the pre-specified statistical criteria for non-inferiority compared to enoxaparin.

Conclusions

The prevention and treatment of thrombosis remains a challenge for patients requiring chronic therapy. Recent policy developments and the availability of new oral

anticoagulants raise the possibility that clinical outcomes may further be improved and support clinicians in their efforts to prevent venous thromboembolism. **BJHM**

Conflict of interest: Professor Kakkar acknowledges the assistance of Rhonda Siddall in the preparation of this article. Professor Kakkar is a consultant to sanofi-aventis, Pfizer, Boehringer Ingelheim, Bayer Schering Pharma and Eisai Inc.

Cohen AT, Agnelli G, Anderson FA et al (2007) Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* **98**(4): 756–64

Department of Health (2008) *Venous thromboembolism (VTE) risk assessment.* Department of Health, London (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_088215 accessed 15 August 2008)

Eriksson BI, Borris LC, Friedman RJ et al (2008) Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip arthroplasty. *N Engl J Med* **358**: 2765–75

Geerts WH, Pineo GF, Heit JA et al (2004) Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* **126**(3 Suppl): 338S–400S

Health Select Committee (2005) *House of Commons – Health - Second Report.* Health Committee Publications, London (www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/99/9902.htm accessed 15 August 2008)

Heit JA (2002) Venous thromboembolism epidemiology: implications for prevention and management. *Semin Thromb Hemost* **28** (Suppl 2): 3–13

Kakkar AK, Brenner B, Dahl OE et al (2008) Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty. *Lancet* **372**: 31–9

Kroegel C, Reissig A (2003) Principle mechanisms underlying venous thromboembolism: epidemiology, risk factors, pathophysiology and pathogenesis. *Respiration* **70**(1): 7–30

Lassen MR, Ageno W, Borris LC et al (2008) Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthoplasty. *N Engl J Med* **358**: 2776–86

National Institute for Health and Clinical Excellence (2007) *Venous thromboembolism (surgical).* National Institute for Health and Clinical Excellence, London (www.nice.org.uk/CG46 accessed 15 August 2008)

National Institute for Health and Clinical Excellence (2008) *Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults.* National Institute for Health and Clinical Excellence, London (www.nice.org.uk/nicemedia/pdf/TA157Guidance.pdf accessed 20 May 2009)

National Institute for Health and Clinical Excellence (2009) *Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults.* National Institute for Health and Clinical Excellence, London (www.nice.org.uk/nicemedia/pdf/TA170Guidance.pdf accessed 19 May 2009)

Pengo V, Lensing AW, Prins MH et al (2004) Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* **350**(22): 2257–64

Turpie AG, Lassen MR, Davidson BL et al (2009) Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* **373**(9676): 1673–80

White RH (2003) The epidemiology of venous thromboembolism. *Circulation* **107**(90231): I4–8

KEY POINTS

- Venous thromboembolism continues to be a leading cause of hospital death affecting many hospitalized patients.
- Despite a conclusive evidence base, adequate venous thromboembolism prophylaxis continues to be routinely overlooked with patients placed at risk.
- The Department of Health's recent risk assessment strategy and the recent National Institute for Health and Clinical Excellence guidance should help to reverse this situation.
- New oral anticoagulants may drive improved clinical outcomes and help to prevent venous thromboembolism.