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Editorial

Rivaroxaban for thromboembolism prophylaxis after orthopaedic surgery

Venous thromboembolism (VTE) causes up to 32 000 deaths each year in the UK at an estimated cost to the NHS of £640 million [1]. This is more than the combined deaths from breast cancer, acquired immunodeficiency syndrome and road traffic accidents, yet it receives little media or even medical coverage. Orthopaedic surgery appears to be associated with the greatest risk of deep vein thrombosis (DVT) and pulmonary embolism, with incidences of approximately 44% (95% CI 42–47%) after elective hip arthroplasty, 37% (95% CI 35–40%) after hip fracture surgery and 27% (95% CI 22–32%) after elective knee arthroplasty [2]. There are an estimated 130 000 major hip and knee surgical procedures annually in the UK (within the NHS) [3]. The national costs from VTE-related morbidity and mortality in orthopaedic surgery are, therefore, considerable. Whatever the diagnostic criteria used for detecting events, this specialty is at the top of the VTE 'league table.'

In 2007, National Institute of Health and Clinical Excellence (NICE) guidelines recommended mechanical (graduated compression stockings) and pharmacological prophylaxis against VTE, with low molecular weight heparin (LMWH) or fondaparinux, in all patients undergoing elective orthopaedic surgery, irrespective of the site of surgery [2] (see Table 1). One might think this practice would be widely accepted and implemented in high-risk groups, but a recent survey would suggest otherwise; only 7% of respondents adhered to NICE guidelines after hip fracture, 44% after hip arthroplasty, and 22% in groups with additional risk factors for VTE [4]. There is evidence of benefit for *extended* postoperative anticoagulation for up to 4 weeks after total hip replacement [5]. On an intention-to-treat analysis, the incidence of VTE was reduced from 34% in controls to 16% in a group treated with 40 $mg.day^{-1}$ enoxaparin for 30 days ($p < 0.001$); the number needed to treat (NNT) to prevent one episode of VTE is, therefore, just over 5. A review of other similar studies suggests that extended prophylaxis (with LMWH) after hospital discharge reduces VTE by approximately 50% [6]. The NICE guidelines for extended postoperative use apply to hip fracture surgery and elective hip arthroplasty associated with other risk factors for VTE, the most

Table 1 Summary of NICE guidelines from 2007 and 2009 for venous thromboembolism (VTE) prophylaxis after orthopaedic surgery [2, 11].

Surgical procedure	Recommended prophylaxis
All elective orthopaedic procedures	Mechanical prophylaxis and either daily subcutaneous enoxaparin *or* fondaparinux while an inpatient
Hip replacement surgery with additional risk factors for VTE*	Mechanical prophylaxis and either daily enoxaparin *or* fondaparinux continued for 4 weeks after surgery *or* rivaroxaban 10 mg once daily, starting 6–10 h after surgery (provided adequate haemostasis has been achieved), continued for 5 weeks
Hip fracture surgery	Mechanical prophylaxis and either daily subcutaneous enoxaparin *or* fondaparinux continued for 4 weeks after surgery
Knee replacement surgery	Mechanical prophylaxis and either daily enoxaparin *or* fondaparinux while an inpatient. *Alternatively*, rivaroxaban 10 mg once daily starting 6–10 h after surgery (provided adequate haemostasis has been achieved), continued for 2 weeks

*Risk factors including but not limited to: age over 60 years; previous history of VTE; immobility; congestive cardiac failure; obesity; recent myocardial infarction/cerebrovascular accident; or inherited thrombophilia.

notable of which is age > 60 years (see Table 1) [2].

Despite the advantages of LMWH (simple regimen, no mandatory monitoring, predictable pharmacokinetics, good overall safety profile) there are significant drawbacks. It is administered parenterally, is not easily reversible, can cause local skin reactions, may result in thrombocytopenia (with a paradoxical increase in the risk of thrombosis), and if given long-term contributes to osteoporosis [7]. Provided they are actually prescribed, there is reasonable compliance with injectable LMWH in the community [8]; however, the hidden costs (for example drug provision, district nurse visits, disposal of sharps) can be high [9]. Their use may also be associated with rebound thrombin generation, reverting to a 'supra-thrombotic' state on withdrawal of treatment [10].

In April 2009, NICE extended its guidelines for elective hip and knee replacement surgery to include the novel agent rivaroxaban (Xarelto®; Bayer plc, Newbury, Berks, UK) as an alternative prophylactic agent against VTE [11]. This use of rivaroxaban, with respect to VTE prophylaxis in orthopaedic surgery, is considered further in this editorial. The 2007 NICE guidelines (including the 2009 amendment) for VTE prophylaxis in orthopaedic surgery are summarised in Table 1. Rivaroxaban is an orally active direct factor Xa inhibitor, preventing the conversion of prothrombin to thrombin. It acts on both free factor Xa and that associated with thrombus (that is, it may also have a role in the *treatment* of VTE). This is important since this thrombin burst is the primary site for amplification of the coagulation cascade [12]. The prevention of the generation of thrombin by rivaroxaban results in its anticoagulant action and is paralleled by prolongation of the prothrombin time and activated partial thromboplastin time in a dose-dependant manner [13]. Rivaroxaban does not appear to affect platelet function.

Rivaroxaban has predictable pharmacokinetics, is absorbed well orally and does not require any dose adjustments for weight, age or sex. Factor Xa is inhibited in a competitive, reversible fashion for approximately 12 h after a single oral dose but thrombin formation is inhibited for 24 h [14, 15], facilitating a once-daily dosing regimen. Rivaroxaban undergoes hepatic metabolism and has both renal and biliary elimination. According to its Summary of Product Characteristics, rivaroxaban does not require any dose adjustments in patients with mild (creatinine clearance 50–80 $ml.min^{-1}$) or moderate (creatinine clearance 30–49 $ml.min^{-1}$) renal impairment, but should be used with caution in patients with severe renal impairment (creatinine clearance 15–29 $ml.min^{-1}$) or moderate renal impairment concomitantly receiving other products that increase rivaroxaban plasma concentrations [16]. It is at least partly metabolised by the cytochrome P_{450} system and there is, therefore, a potential for an interaction with drugs that strongly inhibit cytochrome P_{450} 3A4 (CYP3A4), such as ketoconazole [16, 17]. This appears far less important than with warfarin; indeed, it may not be clinically significant, and there do not appear to be any dietary interactions [13]. Similarly, agents that significantly induce CYP3A4, such as rifampicin, carbemazepine, phenytoin and St John's Wort, may reduce its efficacy [16]. Rivaroxaban should be used with caution in patients with moderate hepatic impairment (Child Pugh B), those treated with other anti-haemostatic agents, ulcerative gastrointestinal disease, recent intracranial haemorrhage, or after spinal or neurosurgery [16].

Early dose-finding studies (phase II) in patients undergoing total knee replacement or total hip replacement showed a flat dose-response curve for rivaroxaban with a similar risk of major haemorrhage (0.7%) to enoxaparin 40 mg (1.9%) when using a 10-mg daily dose [13]. (Major bleeding was defined as fatal bleeding, bleeding into a critical organ, bleeding leading to re-operation or treatment cessation, clinically overt bleeding leading to a ≥ 2 $g.dl^{-1}$ drop in haemoglobin concentration, or bleeding leading to a transfusion of ≥ 2 units of blood). Doses above 10 $mg.day^{-1}$ are associated with increased risk of major bleeding; the 20-mg, 30-mg and 40-mg daily doses caused major bleeding in 4.3%, 4.9% and 5.1% of patients, respectively [18]. The 10-mg daily dose was chosen to represent the optimal balance between efficacy and bleeding [13]. This was

confirmed in a series of subsequent phase III trials. The REgulation of Coagulation in major ORthopaeDic surgery series (RECORD 1–4) studied more than 12 500 patients using this standardised dose for both hip and knee replacement surgery, rivaroxaban starting on the day of operation and continuing for between 10 days and 5 weeks [19–22]. In each of these trials, rivaroxaban reduced the risk of VTE compared with enoxaparin 40 mg daily, with absolute risk reductions of 3% (95% CI 2–4%), 7% (95% CI 5–9%) and 9% (95% CI 6–13%) in RECORD 1–3, respectively [19–22]. It was also shown to be more effective than the larger dose of enoxaparin (30 mg twice daily) used in the USA (RECORD 4) giving an absolute risk reduction of 3% (95% CI 1–6%). Overall, this translates to a NNT (to prevent one VTE) of around 23. In one of these studies, RECORD 2 [20], enoxaparin was given for less than half the duration of rivaroxaban, favouring the novel agent. However, this may correlate more closely with current clinical practice, in which patients may receive thromboprophylaxis as an inpatient but it is stopped on discharge from hospital. Rivaroxaban has not yet been studied in hip fracture surgery and the manufacturer does not recommend its use in this patient group [16]. Deaths from pulmonary embolism in the RECORD studies were grouped with proximal DVT, non-fatal pulmonary embolism and all-cause mortality. When results from RECORD 1–3 are pooled, there is a relative risk reduction of 63% (95% CI 34–79%) translating to a NNT of 123 to prevent one of these outcomes. This is roughly equivalent to the NNT (125) of type-2 diabetic patients with hypertension over a 5-year period to prevent one cardiovascular death [23].

Any benefit from thromboprophylaxis must be weighed against the risk of bleeding in clinical use and it follows that the greater the anticoagulant effect, the higher the incidence of haemorrhage-related morbidity. There do not appear to be any important pharmacokinetic or pharmacodynamic interactions with naproxen or aspirin; however, a prolonged bleeding time was observed with clopidogrel and this is likely to be clinically significant [16]. The manufacturers recommend care with concomitant administration of non-steroidal anti-inflammatory drugs, including aspirin, as there may be patients who show pharmacodynamic interactions that have not yet been identified. Correction of anticoagulation in the event of major bleeding after rivaroxaban has not been tested and no specific antagonist exists. This is a potential drawback, but is offset somewhat by its predictability, in contrast to warfarin. Theoretically, recombinant factor VIIa and prothrombin concentrate may reverse the effects and enable haemostasis in the event of overdose coupled with clinically significant bleeding [15]. The manufacturer recommends waiting at least 18 h after an oral dose before attempting spinal or epidural anaesthesia and at least 6 h should elapse after epidural catheter placement/removal or spinal puncture before the next dose of rivaroxaban is administered; this should be extended to 24 h in the event of a 'traumatic procedure' (presumably a 'bloody' tap) [16]. Theoretically, the prothrombin time should assist in decision-making as it is linearly related to rivaroxaban plasma concentration (correlation coefficient $r = 0.98$) [16].

There are studies investigating the use of rivaroxaban for the prevention of VTE in medical inpatients, treatment of existing DVT and PE, prevention of stroke in patients with atrial fibrillation, and secondary prevention in patients with acute coronary syndromes [13]. Initial results appear promising, with good efficacy and side-effect profiles; however, the current UK licence only extends to the orthopaedic procedures outlined in this editorial. The daily acquisition cost of Xarelto® 10 mg is almost identical to that of Clexane® 40 mg (Sanofi Aventis, Guildford, Surrey, UK): £4.50 and £4.20 respectively [24]. Compared with parenteral heparins and oral vitamin K antagonists (with their unpredictable pharmacokinetics, pharmacodynamics and multiple drug interactions), the practical efficacy of a direct Xa inhibitor provides a real opportunity to reduce thromboembolic events, both in hospital and in the community, after major orthopaedic surgery. In our opinion this opportunity should be embraced, in conjunction with phase IV studies, as this novel agent may prove more revolutionary than first appreciated.

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