Context and Policy Issues

Venous thromboembolism (VTE) can lead to increased morbidity and mortality through the clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE). Patients undergoing major orthopedic surgery — including elective total hip replacement (THR), elective total knee replacement (TKR), and hip fracture surgery (HFS) — have an elevated risk of VTE. As a result, it has become standard practice that patients undergoing major orthopedic surgery receive thromboprophylaxis with an anticoagulant. Dabigatran etexilate (Pradax™) and rivaroxaban (Xarelto®) are anticoagulants that were approved by Health Canada in 2008 for the prevention of VTE in patients who have undergone elective THR or TKR. When compared with other anticoagulants, dabigatran and rivaroxaban offer potential advantages that include fixed once-daily dosing, oral administration, rapid onset of action, low potential for interactions with other drugs, and no requirement for anticoagulation monitoring. However, there are several concerns regarding potential harm from using dabigatran and rivaroxaban, including an increased risk for hepatotoxicity, clinically significant bleeding, and acute coronary events. In light of an increasing trend in major orthopedic surgeries being conducted in Canada, this report reviews the evidence for the clinical-effectiveness and safety of dabigatran and rivaroxaban compared with anticoagulants currently being used in clinical practice for the prevention of VTE after major orthopedic surgery.

Research Question

What is the clinical-effectiveness and safety of dabigatran or rivaroxaban compared to low—molecular-weight heparins (LMWH), unfractionated heparin, warfarin, or fondaparinux for thromboprophylaxis after elective total hip replacement, elective total knee replacement, or hip fracture surgery?

Methods

Published English-language reports of any study, regardless of design, were identified by searching electronic databases between 1999 and April 17, 2009. The websites of regulatory, health technology assessment, and other related agencies were searched for additional reports. Searches were supplemented by hand searching the bibliographies of relevant reports. Two reviewers independently selected articles for inclusion using pre-defined criteria.

Summary of Findings

One systematic review, one phase 2 RCT (BISTRO II), and three phase 3 RCTs (RE-NOVATE, RE-MODEL, and RE-MOBILIZE) compared dabigatran with enoxaparin for thromboprophylaxis after THR or TKR. In the systematic, review-based meta-analysis, pooled results from RE-NOVATE, RE-MODEL, and RE-MOBILIZE (8,210 participants) revealed no statistically significant differences between dabigatran and enoxaparin in any of the end points that were used in the evaluation of safety or efficacy of thromboprophylaxis after THR or TKR. In the RE-NOVATE (3,494 participants; THR) and RE-MODEL (2,101 participants; TKR), dabigatran at doses of 220 mg or 150 mg once daily was judged to be statistically non-inferior to enoxaparin 40 mg once daily for the primary outcome (a composite of total VTE and all-cause mortality). Both doses of dabigatran were judged to be statistically inferior to enoxaparin 30 mg twice daily in the RE-MOBILIZE trial (2,615 participants; TKR). The safety results from all three trials showed that the rates of bleeding, liver enzyme elevations, and acute coronary events with either dose of dabigatran were comparable with those of enoxaparin.
Four phase 2 RCTs and three phase 3 RCTs (RECORD 1 [4,541 participants; THR], RECORD 2 [2,509 participants; THR], and RECORD 3 [2,531 participants; TKR]) compared rivaroxaban with enoxaparin for thromboprophylaxis after TKR or THR. All three phase 3 studies showed the superior clinical-effectiveness of rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily for the primary end point (any DVT, non-fatal PE, and all-cause mortality). The rates of major bleeding, liver enzyme elevations, and acute coronary events were comparable between treatment groups in all three trials. Preliminary unpublished results from a phase 3 trial, RECORD 4 (3,148 participants; TKR), indicate that rivaroxaban 10 mg once daily produces a statistically significant reduction in the incidence of the primary end point (a composite of any DVT, non-fatal PE, and all-cause mortality) when compared with enoxaparin 30 mg twice daily, with low rates of major bleeding in both treatment groups.

Limitations

Patients with severe renal insufficiency, severe liver disease, or at high risk of bleeding were excluded from the reviewed trials. The low numbers of patients with a previous history of VTE, over the age of 75 years, or at extremities of weight limited the generalizability of the results to populations in clinical practice. Clinically important outcomes such as post-DVT complications, length of hospital stay, health-related quality of life, and surgical outcomes were not assessed. The definitions of major bleeding events differed significantly between the dabigatran and rivaroxaban clinical trials, making comparative risk-benefit assessments difficult. More than 25% of patients (except in RE-NOVATE) were excluded from the primary efficacy analysis due to inadequate assessment of thromboembolism by contrast venography. Asymptomatic DVTs (particularly distal) accounted for most of the primary outcome composite events, but the clinical importance of asymptomatic DVTs as a surrogate measure of symptomatic events has not been fully elucidated. The low occurrence of symptomatic VTE, death, and major bleeding events should be interpreted with caution because the trials were not powered to investigate the differences in these low-frequency events. No definitive statements can be made about the safety of rivaroxaban or dabigatran until long-term data from ongoing trials and post-marketing surveillance are available. There have been no head-to-head comparisons of dabigatran or rivaroxaban with each other or with other LMWH, warfarin, unfractionated heparin, or fondaparinux. No trials have yet assessed the safety and efficacy of dabigatran or rivaroxaban for HFS.

Conclusions and Implications for Decision or Policy Making

The evidence that dabigatran is at least as effective as enoxaparin for thromboprophylaxis after THR or TKR is conflicting. Of three published phase 3 trials comparing dabigatran with enoxaparin, two showed non-inferiority for the prevention of VTE after THR or TKR, and the trial comparing dabigatran with the Health Canada-approved dosing regimen for enoxaparin did not. All three phase 3 trials evaluating rivaroxaban showed superior clinical-effectiveness over enoxaparin for the prevention of VTE after THR or TKR. Based on phase 3 trial findings, the Canadian Expert Drug Advisory Committee (CEDAC) recommended that rivaroxaban, but not dabigatran, be listed in publicly funded drug plans for the prophylaxis of VTE after TKR or THR.

There are no head-to-head trials comparing rivaroxaban with dabigatran, or comparing either drug to other anticoagulants. As a result, indirect comparisons should be interpreted with caution because of differences in the methods for assessing outcomes among trials. There is no evidence to support the use of dabigatran or rivaroxaban in patients undergoing HFS. In March 2009, an advisory committee recommended that the United States Food and Drug Administration (FDA) approve rivaroxaban for thromboprophylaxis after TKR or THR while considering data that suggested increased bleeding, hepatotoxicity, and number of cardiovascular events. In conclusion, although some efficacy and safety data for dabigatran and rivaroxaban are available, data from additional trials and post-marketing surveillance will be needed to characterize the role of these anticoagulants for thromboprophylaxis in diverse patient populations after major orthopedic surgery.