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Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty☆

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ABSTRACT

Introduction: The RECORD programme compared oral rivaroxaban with enoxaparin for prevention of venous thromboembolism after elective total hip or knee replacement. This analysis compared the safety of concomitant use of specified medications with rivaroxaban and enoxaparin by evaluating postoperative bleeding rates from the pooled RECORD1–4 data.

Materials and methods: The co-medications were non-steroidal anti-inflammatory drugs and platelet function inhibitors, including acetylsalicylic acid (no dose restriction). The endpoints evaluated were the composite of major and non-major clinically relevant bleeding and any bleeding occurring after first oral study drug intake. The time relative to surgery was stratified into three time periods: day 1–3, day 4–7 and after day 7. Relative bleeding rate ratios for co-medication use versus non-use were derived using stratified Mantel–Haenszel methods and compared between rivaroxaban and enoxaparin groups.

Results: Co-medication use with rivaroxaban or enoxaparin resulted in non-significant increases in bleeding events. Respective rate ratios were not significantly different between rivaroxaban and enoxaparin for all bleeding endpoints with concomitant use of non-steroidal anti-inflammatory drugs (any bleeding, 1.22 vs 1.22; major and non-major clinically relevant bleeding, 1.28 vs 0.90) and with concomitant use of platelet function inhibitors/acetylsalicylic acid (any bleeding, 1.32 vs 1.40; major and non-major clinically relevant bleeding, 1.11 vs 1.13).

Conclusions: This explorative analysis indicates that there is no significant increase in bleeding risk for rivaroxaban compared with enoxaparin when co-administered with non-steroidal anti-inflammatory drugs or acetylsalicylic acid, although, because of low usage, the experience with platelet function inhibitors (except acetylsalicylic acid) was limited.

Introduction

Patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) are at significantly increased risk of developing venous thromboembolism (VTE), and the routine use of anticoagulant prophylaxis is recommended in these patients. Current evidence-based guidelines, including those from the American College of Chest Physicians, recommend the use of a low molecular weight heparin (e.g. enoxaparin), fondaparinux (Arixtra; GlaxoSmithKline: Research Triangle Park, NC, USA) or vitamin K antagonists (e.g. warfarin) to prevent postoperative VTE after THA or TKA [1]. To address some of the well-known limitations of these established agents, several new oral anticoagulants have been developed [2], including the direct Factor Xa inhibitor rivaroxaban (Xarelto; Bayer Pharma AG: Berlin, Germany). Rivaroxaban has been approved in more than 110 countries worldwide for the prevention of VTE in adult patients after elective hip or knee replacement surgery. In the phase III RECORD (REgulation of Coagulation

Abbreviations: ASA, acetylsalicylic acid; ATC, Anatomical Therapeutic Chemical Classification; bid, twice daily; CI, confidence interval; CrCl, creatinine clearance; NMCR, non-major clinically relevant; NSAIDs, non-steroidal anti-inflammatory drugs; od, once daily; PFIs, platelet function inhibitors; TKA, total knee arthroplasty; THA, total hip arthroplasty; VTE, venous thromboembolism.

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in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) programme, which enrolled more than 12,500 patients in four studies, rivaroxaban demonstrated superior efficacy to enoxaparin for the prevention of VTE in this setting, without a significant increase in major bleeding [3–6].

In most phase III clinical trials of the use of anticoagulants after THA or TKA, the primary safety endpoints investigated are major bleeding events. In addition to these events, there are several other safety issues that may be relevant to everyday clinical practice. Among these concerns are potential interactions with other drugs; these interactions are a considerable burden associated with the use of vitamin K antagonists. Interactions with drugs that affect haemostasis are of particular interest because of the potential effect on bleeding risk; these include non-steroidal anti-inflammatory drugs (NSAIDs), platelet function inhibitors (PFIs) and other anticoagulants. It is estimated that approximately 30 million people worldwide take NSAIDs and/or acetylsalicylic acid (ASA) on a daily basis [7]. In the US alone, more than 111 million prescriptions for NSAIDs are made each year [8], with many more people taking these as over-the-counter drugs, and approximately one-third of individuals aged 65 or over are reported to take NSAIDs on a daily basis [8]. These drugs are used for their analgesic, anti-inflammatory and antipyretic properties, and ASA is also prescribed for the prevention and treatment of cardiovascular disease and the prevention of stroke in at-risk patients. Moreover, perioperative myocardial infarction is a significant cause of morbidity and mortality after THA or TKA [9]; therefore, ASA is often given with thromboprophylaxis and interruption of ASA therapy is not recommended in patients undergoing orthopaedic surgery. NSAIDs are frequently used as pain relief in patients with osteoarthritis or rheumatoid arthritis [10,11], or osteophytes around a hip prosthesis, and are recommended for analgesia after THA or TKA [12,13]. Patients undergoing THA or TKA are also recommended to receive anticoagulants for postoperative VTE prevention according to guidelines [1]. Sole use of either class of drug is associated with certain risks: NSAID use can lead to gastrointestinal ulcers and bleeding [14,15], and, by their nature, anticoagulants can increase the risk of bleeding. With the emergence of new oral anticoagulants, safety data on the potential risks of concomitant use of NSAIDs with these agents will be required, particularly on the risk of bleeding in the postoperative setting.

Potential interactions between rivaroxaban and NSAIDs and ASA have been investigated in healthy young subjects [16,17]. In the RECORD programme, the concomitant use of rivaroxaban and NSAIDs, including ASA and other PFIs, was permitted in accordance with the study protocol. The objective of this analysis was to investigate the safety of concomitant use of rivaroxaban and these medications compared with enoxaparin by evaluating the incidence of postoperative bleeding events in patients undergoing THA or TKA in the RECORD programme.

Materials and methods

Study design

This analysis was part of a prespecified analysis of pooled data from the four phase III studies of the RECORD programme. In a double-dummy design, patients were randomised to receive either oral rivaroxaban 10 mg once daily (od) starting 6–8 hours after surgery or subcutaneous enoxaparin 40 mg od starting 12 hours before surgery (RECORD1–3) [3–5] or enoxaparin 30 mg twice daily (bid) starting 12–24 hours after wound closure or after adequate haemostasis was achieved (RECORD4) [6]. Patients undergoing THA received oral rivaroxaban for 31–39 days or subcutaneous enoxaparin for 31–39 days (RECORD1) or enoxaparin for 10–14 days with placebo tablets for 31–39 days (RECORD2); patients undergoing TKA (RECORD3 and RECORD4) received rivaroxaban or enoxaparin for 10–14 days [3–6].

Specified co-medications

The co-medications investigated in this prespecified analysis were NSAIDs and PFIs or ASA. PFIs and ASA were grouped together as one of the prespecified classes of co-medications and, therefore, outcomes were not recorded for PFIs and ASA separately. The co-medications documented in the case report forms were coded according to the World Health Organization Drug Dictionary, version 2005/Q3, in which NSAIDs were coded as anti-inflammatory and antirheumatic products, non-steroids (Anatomical Therapeutic Chemical Classification [ATC] code M01A), and PFIs or ASA were coded as PFIs excluding heparin (ATC code B01AC) and/or multiple-ingredient drugs containing ASA. There was no limitation on the choice of a specific drug or dose of NSAIDs and PFIs or ASA in the study protocols. These analyses and the definition of co-medications were prespecified in the RECORD1–4 pooled statistical analysis plan prior to unblinding of any of the RECORD studies.

Analysis of bleeding endpoints

Potential drug–drug interactions were investigated by analysis of prespecified adjudicated bleeding endpoints in all patients who underwent surgery and received study medication. The endpoints evaluated were the composite of major and non-major clinically relevant bleeding, and any bleeding occurring after first postoperative oral study drug intake (rivaroxaban or matching placebo tablet). No other safety endpoints were analysed in this investigation. These events were analysed in the at-risk period, which was from the day of surgery (defined as day 1) until 2 days after the last intake of study drug or until event onset, whichever came first. This included the placebo phase of the RECORD2 study. The use of co-medications was considered a time-dependent covariate because patients could stop and restart the co-medications of interest in the evaluated risk period. The time relative to surgery was stratified into three time periods: day 1–3, day 4–7 and after day 7. This was based on the consideration that the risk of a first bleeding event decreases over time after surgery and the prevalence of co-medication use may vary over time. However, the bleeding risk was assumed to be constant within each time period to allow the application of patient–time-based approaches.

Relative bleeding rates were calculated for each time period, as well as for the entire at-risk period, and expressed as rates per 100 patient-weeks. The time at-risk with co-medication use was prespecified as a patient's time under co-medication use plus the 2 days following the cessation of the co-medication, if it was stopped. Relative bleeding rate ratios for co-medication use versus non-use were derived using stratified Mantel–Haenszel methods and compared between rivaroxaban and enoxaparin/placebo groups.

Results

Patients concomitantly receiving either NSAIDs, or PFIs or ASA were similarly distributed between the rivaroxaban and enoxaparin/placebo groups (Table 1). The characteristics of these patients (gender, age, weight) were similar between the rivaroxaban and enoxaparin/placebo groups (Table 1). Over 70% of patients in both groups concomitantly used NSAIDs (at least once) in the time period of interest. PFIs or ASA were taken at least once by 9% of patients in both groups (Table 1), although less than 1% of patients in each group took the potent PFIs clopidogrel or ticlopidine.

The proportion of patient–time with NSAID co-medication use decreased over time and was similar in both groups (days 1–3: 62% vs 62%; days 4–7: 51% vs 52%; after day 7: 29% vs 28%, for rivaroxaban and enoxaparin/placebo, respectively). The proportion of patient–time