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Safety and Efficacy of Edoxaban, an Oral Factor Xa Inhibitor, Versus Enoxaparin for Thromboprophylaxis After Total Knee Arthroplasty: The STARS E-3 Trial

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ABSTRACT

Introduction: This phase 3 trial compared the safety and efficacy of edoxaban, an oral direct factor Xa inhibitor, with enoxaparin sodium (enoxaparin) for thromboprophylaxis after total knee arthroplasty (TKA) in patients in Japan and Taiwan.

Materials and methods: In this randomized, double-blind, double-dummy study, patients received oral edoxaban 30 mg once daily beginning 6 to 24 hours postsurgery or enoxaparin 2000 IU (equivalent to 20 mg) subcutaneously twice daily beginning 24 to 36 hours postsurgery for 11 to 14 days. The primary efficacy endpoint was the composite of symptomatic pulmonary embolism and symptomatic and asymptomatic deep vein thrombosis. Safety endpoints included the incidence of major bleeding, clinically relevant non-major (CRNM) bleeding, major bleeding or CRNM bleeding, all bleeding events, adverse events, and adverse drug reactions.

Results: Of 716 patients enrolled, 360 and 356 were randomized to receive edoxaban or enoxaparin, respectively. The primary efficacy outcome occurred in 22/299 (7.4%) and 41/295 (13.9%) patients in the edoxaban and enoxaparin groups, respectively (relative risk reduction = 46.8%), indicating non-inferiority ($P < 0.001$) and superiority ($P = 0.010$) of edoxaban versus enoxaparin. In the edoxaban and enoxaparin groups, major bleeding occurred in 4/354 (1.1%) versus 1/349 (0.3%) patients ($P = 0.373$); major or CRNM bleeding occurred in 22/354 (6.2%) versus 13/349 (3.7%) patients ($P = 0.129$), respectively.

Abbreviations: ADR, adverse drug reaction; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; FAS, full analysis set; GCP, Good Clinical Practice; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; LMWH, low-molecular weight heparin; PE, pulmonary embolism; PK, pharmacokinetics; PPS, per protocol set; THA, total hip arthroplasty; TKA, total knee arthroplasty; SD, standard deviation; STARS-E3, Studying Thrombosis After Replacement Surgery; ULN, upper limit of normal; VTE, venous thromboembolism.

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Conclusions: Edoxaban 30 mg once daily was more effective for thromboprophylaxis than subcutaneous enoxaparin 2000 IU twice daily following TKA and demonstrated a similar incidence of bleeding events.

Introduction

Anticoagulants are administered to reduce the incidence of thromboembolic events after major orthopaedic surgery such as total knee arthroplasty (TKA). In Japan, unfractionated heparin and warfarin are used with caution for venous thromboembolism (VTE) prevention due to limited evidence regarding their efficacy in postoperative deep vein thrombosis (DVT) prevention, adverse drug reactions, and the risk of bleeding in this patient population. Current Japanese guidelines recommend either anticoagulant therapy with the low-molecular weight heparin (LMWH) enoxaparin or the synthetic pentasaccharide indirect factor Xa inhibitor fondaparinux, or intermittent pneumatic compression for patients following orthopaedic surgery [1,2]. However, enoxaparin and fondaparinux require parenteral administration [3,4]. As a result, there is a need for more convenient anticoagulants.

Edoxaban is a novel, oral, direct factor Xa inhibitor that has been evaluated for stroke prevention in atrial fibrillation as well as treatment and secondary prevention of recurrent VTE [5,6]. Edoxaban displays predictable pharmacokinetics (PK) at daily doses of ≤150 mg with approximately 62% oral bioavailability [7,8]. In a phase 2 study of Japanese patients undergoing TKA, edoxaban doses of 5 mg to 60 mg once daily demonstrated significant dose-related reductions in VTE with a low incidence of bleeding that did not increase with increasing dose [9]. Three phase 3 studies have evaluated the safety and efficacy of edoxaban compared with enoxaparin for the prevention of VTE following TKA, total hip replacement, and after hip fracture surgery [10,11]. The present phase 3 study, Studying Thrombosis After Replacement Surgery (STARS-E3; clinicatrials.gov NCT01181102), was a multicenter, randomized, double-blind trial comparing the efficacy and safety of oral edoxaban 30 mg once daily with subcutaneous enoxaparin 2000 IU (equivalent to 20 mg) twice daily following TKA in Japanese and Taiwanese patients.

Methods

Patients

Men and women aged 20 to 84 years who were scheduled to undergo unilateral TKA, excluding revision arthroplasty, were eligible for inclusion in the study. Patients were ineligible if they had increased risk of bleeding; were at high risk for thromboembolism; had a body weight <40 kg; severe renal impairment (creatinine clearance <30 mL/min); hepatic dysfunction; or were pregnant or lactating women. Postoperative exclusion criteria included abnormal bleeding from the injection site upon administration of spinal anaesthesia; abnormal or excessive bleeding during or immediately following surgery; and the inability to take oral medications. Subjects in whom the epidural catheter could not be removed by 2 hours prior to initiation of study drug administration were excluded in order to avoid risk of epidural or spinal hematomas associated with anticoagulation and neuraxial anesthesia. The concomitant use of anticoagulants, antiplatelet agents, thrombolytic agents, and other agents that affect thrombus formation was not allowed during the period from the day of surgery until 24 hours after the final dose of the study drug, unless treatment of DVT or PE was required.

Study design and medications

Patients were randomly assigned to a study group using the block allocation method with the site as a block (block size of 4) in a 1:1 allocation ratio (edoxaban:enoxaparin). According to the key code, patients were randomly allocated numbers that were generated using the SAS function RANUNI to obtain a single stream of random numbers that were transferred from SAS to Excel. Using a double-blind, double-dummy design, 716 patients were assigned to receive either oral edoxaban 30 mg once daily or subcutaneous enoxaparin 2000 IU every 12 hours (twice daily) for 11 to 14 days. Enoxaparin 2000 IU twice daily is the usual recommended dose for adults in Japan, a dose lower than that used in the West, based on the lower body weight of Japanese patients [12]. Edoxaban or edoxaban placebo was initiated 6 to 24 hours following surgery. Enoxaparin or enoxaparin placebo was initiated 24 to 36 hours following surgery (Japanese standard of care). The use of mechanical methods of prophylaxis (i.e., intermittent pneumatic compression therapy of the foot sole or of the lower leg and thigh, and the use of elastic stockings) was permitted from the day of surgery to venography.

Venography of the operated lower limb was performed within 24 hours after the last dose of study medication, or within 96 hours if it could not be performed within 24 hours for reasons such as difficulty in establishing an intravenous line. Patients had a follow-up visit 25 to 35 days after the last dose of the study drug. In addition to the planned post-treatment venography, if symptomatic DVT or PE was suspected based on signs or symptoms that occurred during the period from initiation to venography at completion (discontinuation) of study drug administration, appropriate imaging was performed to confirm the event. Suspected DVT was evaluated by ultrasonography, venography, and/or CT scanning, among other techniques. Suspected PE was confirmed by pulmonary scintigraphy, pulmonary arteriography, and/or CT scanning. A definite diagnosis of symptomatic DVT or PE was based on the clinical imaging findings. Treatment compliance was verified by patient interview and assessment of residual drugs.

The study was performed in accordance with the provisions of the Declaration of Helsinki, MHW Ordinance on Good Clinical Practice (GCP) or Guideline for GCP, and other related regulations. The protocol was approved by the institutional review board at each center and written informed consent was obtained from all patients prior to randomization.

Outcome Measures

All thromboembolic events were evaluated by the Thromboembolic Events Evaluation Committee based on copies of the clinical findings, such as films, provided by the principal investigator or co-investigator to the sponsor under blinded conditions. Evaluation by the committee was defined as the final evaluation. The primary efficacy endpoint was the composite of symptomatic PE and symptomatic and asymptomatic DVT. A secondary efficacy outcome was the proportion of patients with one or more of the following thromboembolic events: symptomatic DVT, proximal DVT, symptomatic PE, or VTE-related mortality. Other secondary efficacy outcomes included the incidence of asymptomatic or symptomatic DVT, symptomatic DVT or proximal DVT, symptomatic PE, VTE-related mortality, and all-cause mortality.

Safety endpoints included the incidence of major bleeding, clinically relevant non-major (CRNM) bleeding, major, or CRNM bleeding, all bleeding events (major, CRNM, and minor bleeding), adverse events (AEs), and adverse drug reactions (ADRs). The Bleeding Events Evaluation Committee re-evaluated the validity of the bleeding events evaluated by the principal investigator or co-investigator under blinded conditions, and the evaluation by the committee was defined as the final evaluation. Major bleeding was defined as fatal bleeding, clinically apparent bleeding with a decrease in haemoglobin of more than 2 g/dL,