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REVIEW

Edoxaban for prevention of venous thromboembolism after major orthopedic surgery

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Abstract: Fatal pulmonary thromboembolism is the most serious complication following surgery. Patients undergoing major orthopedic surgeries, including total hip replacement, total knee replacement, and hip fracture surgery, represent a group at particularly high risk of venous thromboembolism. Therefore, prophylaxis for thromboembolic events has been of great concern to surgeons. Edoxaban is a novel, orally available, and highly specific and direct factor Xa inhibitor. This new agent was approved for the prevention of venous thromboembolism in patients undergoing major orthopedic surgery, including total hip replacement, total knee replacement, and hip fracture surgery, by the Japanese Ministry of Health, Labor, and Welfare in 2011. Preclinical and Phase I clinical trials demonstrated several promising properties. Its rapid absorption and short life-time in blood are known. Edoxaban inhibits factor Xa activity directly and selectively. It also has a strong antithrombotic effect without any influence of food intake. Coagulation monitoring is not required. Edoxaban has predictable linear pharmacokinetic and pharmacodynamic profiles. Phase II and III clinical trials have been completed to examine its efficacy and safety in patients undergoing major orthopedic surgery. In these clinical trials, oral administration of edoxaban showed efficacy superior to that of oral placebo or subcutaneously administered dalteparin or enoxaparin. Edoxaban can be regarded as a first choice to prevent venous thromboembolism after major orthopedic surgery.

Keywords: edoxaban, thromboprophylaxis, venous thromboembolism, total hip replacement, total knee replacement, hip fracture surgery

Introduction

Venous thromboembolism, ie, deep vein thrombosis and pulmonary embolism, is an important cause of death in hospitalized patients, and treatment of nonfatal symptomatic venous thromboembolism and related long-term morbidities is associated with a considerable cost to the health care service.[1] Venous thromboembolism is a potentially fatal disease.[2,3] Patients undergoing major orthopedic surgery, which includes total hip replacement, total knee replacement, and hip fracture surgery, are a group at particularly high risk for venous thromboembolism[4,5] and fatal pulmonary embolism, which is a catastrophic complication of major orthopedic surgery.[6] Most pulmonary emboli are thought to develop from deep vein thromboses.[5,7–9] The incidence of venous thromboembolism is 0.05%–0.2% in the general community.[10–13] The incidence of total venographically detected deep vein thrombosis 7–14 days following total hip replacement, total knee replacement, and hip fracture surgery in prospective clinical trials in which patients received no thromboprophylaxis or placebo has been 42%–57%,[14–22] 41%–85%,[14,23–30] and 46%–60%,[14,31–33] respectively. The prevalence

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of fatal pulmonary embolism derived from prospective studies that may have used thromboprophylaxis is 0.1%–2.0%,[14,18,34–38] 0.1%–1.7%,[6,14,31,36,39,40] and 0.3%–7.5%[14,18,33,41] in patients undergoing total hip replacement, total knee replacement, and hip fracture surgery, respectively.

Pulmonary embolism is the most common preventable cause of hospital death and the number one strategy to improve patient safety in hospitals.[4] Therefore, prophylaxis of deep vein thrombosis, especially proximal deep vein thrombosis, which has the potential to develop into pulmonary embolism, has been of great concern to surgeons. The worldwide clinical guidelines, including those from the American College of Chest Physicians,[4] National Institute for Health and Clinical Excellence,[1] and American Association of Orthopedic Surgeons,[42] recommend mechanical and/or pharmacological thromboprophylaxis for the prevention of deep vein thrombosis in patients undergoing major orthopedic surgery. Those guidelines are summarized along with the differences between the recommendations, but all guidelines accept that the most important goal of thromboprophylaxis is to prevent fatal pulmonary embolism.[43]

Warfarin and unfractionated heparin have been used as standard anticoagulants for the prevention and treatment of embolism for over 50 years.[4,44–47] Recently, the low molecular weight heparins or synthetic pentasaccharide, fondaparinux, which indirectly inhibits activated factor X (factor Xa), have been used for prevention of deep vein thrombosis after major orthopedic surgery.[4,44,45,48,49] However, warfarin has numerous clinically important limitations, including slow onset and offset of action, narrow therapeutic windows, and a high degree of interindividual and intraindividual variation of response requiring routine coagulation monitoring, and multiple food-drug and drug-drug interactions.[50–52] An objection to using chemical deep vein thrombosis prophylaxis is the increased risk of bleeding as a result of anticoagulation. The estimated baseline risk of major or significant bleeding in the absence of chemical deep vein thrombosis prophylaxis is 2%.[1] The benefit of deep vein thrombosis prophylaxis has to be weighed against the risks and consequences of postoperative bleeding. The heparins are also associated with an increased risk of bleeding,[53] as well as nonhemorrhagic side effects, such as heparin-induced thrombocytopenia[49,54,55] and osteoporosis.[49] Moreover, the response to fixed doses of unfractionated heparin is unpredictable because of binding to plasma proteins.[53] Low molecular weight heparin preparations have more predictable pharmacokinetic and pharmacodynamic properties, a longer half-life than heparin in blood, and a lower risk of nonhemorrhagic side effects. Fondaparinux catalyzes inhibition of factor Xa. Heparin-induced thrombocytopenia and osteoporosis are unlikely to occur because fondaparinux binds only to antithrombin. Fondaparinux has a longer half-life than low molecular weight heparin. However, heparins and fondaparinux are only available for parenteral administration.[49]

Edoxaban tosylate hydrate (edoxaban, Lixiana®, the free base of DU-176b, Daiichi Sankyo Co Ltd, Tokyo, Japan) is a novel, orally available, and highly specific and direct inhibitor of factor Xa.[56,57] Factor Xa has a critical role in the coagulation cascade, because it is generated at the convergence point of the intrinsic and extrinsic coagulation pathways from direct activation of factor X by tissue factor.[58] Therefore, factor Xa has been thought to represent a promising target for prophylaxis and treatment of thromboembolic diseases.

Edoxaban 15 mg and 30 mg tablets were approved for prevention of deep vein thrombosis in patients undergoing total hip replacement, total knee replacement, and hip fracture surgery by the Japanese Ministry of Health, Labor, and Welfare in April 2011 and launched in July 2011 in Japan.[59] In this paper, we review the results of clinical trials carried out with edoxaban for prevention of deep vein thrombosis after major orthopedic surgery.

The present review includes: in vitro and/or in vivo studies performed prior to clinical studies, which were presented or published, including meeting abstracts; Phase I studies that have examined the clinical safety, tolerability, pharmacokinetics, and/or pharmacodynamics in healthy subjects; studies that have included patients undergoing major orthopedic surgery and evaluated the efficacy and safety of edoxaban for the prevention of deep vein thrombosis; and Phase II and III studies with a randomized design and control groups, providing a direct comparison between different dosages of edoxaban or between edoxaban and a comparator.

Preclinical studies

The potent anti-factor Xa activity and dose-dependent inhibition of thrombosis by edoxaban have been well characterized in nonclinical studies. In vitro, edoxaban demonstrated 10,000-fold selectivity relative to inhibition of thrombin.[60] Inhibition of human factor Xa by edoxaban was concentration-dependent and competitive, with inhibition constant (Ki) values of 0.561 nM.[57] In rats and rabbits, edoxaban exerted significant and dose-dependent anti-factor Xa activity in plasma.[57,60] Edoxaban dose-dependently inhibited thrombus formation in vitro and in vivo.[57,60,61] Prothrombin time was prolonged in a concentration-dependent

and dose-dependent manner.[57,60] Edoxaban also prolonged activated partial thromboplastin time and = prothrombin time in human plasma in a concentration-dependent manner.[57,60] Edoxaban exhibited high oral bioavailability in rats and monkeys and antithrombotic effects in both venous and arterial models of thrombosis in rats.[60] There was significant factor Xa inhibition activity in rat plasma 30 minutes after oral administration of edoxaban, indicating a fast onset of action.[57,61] In monkeys, edoxaban also elicited rapid onset of antifactor Xa activity, reaching a peak at 4 hours and persisting for 24 hours after dosing.[57] Comparisons of the antithrombotic and hemorrhagic effects of edoxaban with those of dalteparin (low molecular weight heparin), unfractionated heparin, and warfarin in rat models indicated that the therapeutic dose range of edoxaban would be wider than that of other anticoagulants.[61] These results demonstrate that edoxaban is a potent and highly selective direct factor Xa inhibitor and might be a promising oral anticoagulant for the prophylaxis and treatment of thromboembolic disease.

Phase I studies

In a Phase I study, the effect of a single 60 mg dose of edoxaban on ex vivo thrombus formation and on factor Xa activity was examined in young healthy subjects.[56] Peak plasma levels of edoxaban were observed at 1.5 hours after oral administration, corresponding to maximum anti-factor Xa activity, which came down at 5 hours and returned to baseline levels after 12 hours. The greatest antithrombotic effect was similarly observed at 1.5 hours, while the effect was significant even at 5 hours. Edoxaban demonstrated strong antithrombotic properties. Inhibition of factor Xa led to a corresponding reduction in generation of thrombin. Edoxaban demonstrated a strong antithrombotic effect, with rapid onset of action and a short-life.

Another Phase I study examined the clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of ascending single and multiple oral doses of edoxaban in healthy male volunteers.[62] Edoxaban was rapidly absorbed, with a peak drug concentration time of 1–2 hours and a half-life ranging from 5.8 to 10.7 hours. Low intersubject and intrasubject variability of plasma edoxaban concentrations was observed. Single-dose administration of edoxaban exhibited dose-dependent effects on activated partial thromboplastin time, prothrombin time, international normalized ratio, and anti-factor Xa activity. There were no clinically significant effects of food on the pharmacokinetics and pharmacodynamics.[63] Edoxaban was safe and well tolerated in single doses up to 150 mg and multiple doses up to 120 mg/day for 10 days, with no dose-dependent increase in drug-related adverse events. Edoxaban appears to have predictable and consistent pharmacokinetic and pharmacodynamic profiles across doses, with low intersubject variability and dose linearity. The predictable pharmacokinetic and pharmacodynamic profiles of edoxaban, lack of a food effect, and low plasma protein binding suggest that coagulation monitoring might not be required for this agent. In another study which enrolled healthy elderly volunteers, oral administration of edoxaban resulted in effective inhibition of factor Xa and thrombin generation, and was well tolerated.[64] There were no serious adverse events. These characteristics suggested that edoxaban might provide consistent anticoagulation for a wide range of patients.

Phase IIa study of blood clot prevention in total hip replacement

Based on the wealth of available preclinical data and promising results of Phase I studies, a multicenter, multinational, open-label, dose-ranging Phase IIa study of the efficacy, safety, and tolerability of oral edoxaban administered once or twice daily was initiated in adult patients undergoing total hip replacement (NCT00107900 http://www.clinicaltrials.gov).[65] This trial enrolled approximately 600 patients to receive once or twice daily oral doses of edoxaban. The trial was reportedly completed in July 2005, but no data are currently available.[65,66]

Phase IIb study of venous thromboembolism prevention in total hip replacement

A randomized, parallel-group, double-blind, double-dummy, multicenter, multinational, multidose Phase IIb study assessed the clinical utility of edoxaban for prevention of deep vein thrombosis compared with dalteparin, a low molecular weight heparin, in patients undergoing elective total hip replacement (NCT00398216 http://www.clinicaltrials.gov, Table 1).[67] The doses of edoxaban evaluated were 15, 30, 60, and 90 mg given orally once daily. The comparator regimen of subcutaneous dalteparin involved an initial dose of 2500 IU followed by 5000 IU once daily thereafter. Both the oral and subcutaneous study medications were started 6–8 hours postoperatively and continued for 7–10 days postoperatively, at which time patients were evaluated at an end of treatment visit. Deep vein thrombosis was examined by bilateral venography at 7–10 days postoperatively and within 24 hours of the last dose of study medication. A total of 903 patients were enrolled. Patients were recruited

Table 1 Summary of clinical trials of edoxaban in development for the prevention of deep vein thrombosis after major orthopedic surgery

Indication phase/trial (government identifier)	Design	Location	Treatment (Edoxaban versus comparator)	Patient number
THR				
Phase IIb/nameless (NCT000398216)[67]	Randomized, parallel-group, double-blind, double-dummy, dalteparin-controlled, multidose, multicenter, multinational	US, Canada, Russia, Ukraine, Denmark, Latvia, UK	Edoxaban 15, 30, 60, 90 mg once daily versus dalteparin initial dose of 2500 IU followed by 5000 IU once daily for 7–10 days	903
Phase IIb/STARS J-2 (NCT01203098)[69]	Randomized, parallel-group, double-blind, open-label, enoxaparin-controlled, multidose, multicenter	Japan, Taiwan	Edoxaban 15, 30 mg once daily versus enoxaparin 20 mg twice daily for 11–14 days	264
Phase III/STARS J-5 (NCT01181167)[70]	Randomized, parallel-group, double-blind, double-dummy, enoxaparin-controlled, noninferiority, multicenter	Japan	Edoxaban 30 mg once daily versus enoxaparin 20 mg twice daily for 11–14 days	610
TKR				
Phase IIb/STARS J-1 (NCT01203072)[68]	Randomized, parallel-group, double-blind, placebo-controlled, dose-ranging, multicenter	Japan	Edoxaban 5, 15, 30, 60 mg once daily versus placebo oral tablet once daily for 11–14 days	523
Phase III/STARS E-3 (NCT01181102)[71]	Randomized, parallel-group, double-blind, double-dummy, enoxaparin-controlled, noninferiority, multicenter	Japan, Taiwan	Edoxaban 30 mg once daily versus enoxaparin 20 mg twice daily for 11–14 days	716
HFS				
Phase III/STARS J-4 (NCT01181141)[72]	Randomized, open-label, enoxaparin-controlled, multicenter	Japan	Edoxaban 30 mg once daily versus enoxaparin 20 mg twice daily for 11–14 days	92

Abbreviations: THR, total hip replacement; TKR, total knee replacement; HFS; hip fracture surgery.

from 53 sites, including the US, Canada, Russia, Ukraine, Denmark, Latvia, and UK. More than 75% of patients were recruited from Russia and Ukraine. The final distribution among the treatment groups was 170, 151, 158, 151, and 144 patients in the edoxaban 15 mg, 30 mg, 60 mg, 90 mg, and dalteparin groups, respectively. Patients who developed symptoms or signs suggestive of deep vein thrombosis prior to planned venography underwent objective testing using either ultrasonography or venography. Patients who developed symptoms or signs suggestive of pulmonary embolism underwent objective testing with computed tomographic pulmonary angiography, ventilation-perfusion lung scanning, or direct pulmonary angiography. Total deep vein thrombosis was defined as the composite of both proximal and distal deep vein thrombosis detected by venography and symptomatic deep vein thrombosis or pulmonary embolism documented by objective testing. Major deep vein thrombosis was defined as the presence of one or more of symptomatic or asymptomatic proximal deep vein thrombosis, symptomatic nonfatal deep vein thrombosis, or death from any cause. Proximal deep vein thrombosis was defined as thrombosis involving the popliteal or more proximal veins. The incidence of total deep vein thrombosis was 28.2%, 21.2%, 15.2%, 10.6%, and 43.8% in the edoxaban 15 mg, 30 mg, 60 mg, 90 mg, and dalteparin groups, respectively (Table 2). The incidence of major deep vein thrombosis was 6.5%, 3.3%, 1.9%, 1.3%, and 13.9% in the edoxaban 15 mg, 30 mg, 60 mg, 90 mg, and dalteparin groups, respectively. The incidence of any proximal deep vein thrombosis was 6.5%, 3.3%, 1.3%, 1.3%, and 13.9% in the edoxaban 15 mg, 30 mg, 60 mg, 90 mg, and dalteparin groups, respectively. There was a statistically significant lower incidence of total deep vein thrombosis in each of the edoxaban dose groups compared with the dalteparin group. There was also a statistically significant dose-response for efficacy across the edoxaban dose groups for efficacy of both total deep vein thrombosis and major deep vein thrombosis. The incidence of the composite of major and clinically relevant nonmajor bleeding was 1.6%, 1.8%, 2.2%, 2.3%, and 0% in the edoxaban 15 mg, 30 mg, 60 mg, 90 mg, and dalteparin groups, respectively, and 95% confidence intervals that broadly overlapped (Table 3). The incidence of all bleeding was 2.1%, 1.8%, 4.9%, 4.0%, and 0.6% in

Table 2 Incidences of total venous thromboembolism in Phase IIb and III studies of edoxaban for the prevention of venous thromboembolism after major orthopedic surgery

Indication phase/trial	Edoxaban[a]					Dalteparin[b]	Enoxaparin[c]	Placebo
	5 mg	15 mg	30 mg	60 mg	90 mg			
THR								
Phase IIb/no name[67] n/N (%)	–	48/170 (28.2)	32/151 (21.2)	24/158 (15.2)	16/151 (10.6)	63/144 (43.8)	–	–
95% CI		21.6 –35.6	15.0–28.6	10.0–21.8	6.2–16.6	35.5–52.3		
P value versus dalteparin		0.005	<0.001	<0.001	<0.001			
Phase IIb/STARS J-2[69] n/N (%)	–	3/78 (3.8)	2/72 (2.8)	–	–	–	3/74 (4.1)	–
Phase III/STARS J-5[70] n/N (%)	–	–	6/255 (2.4)	–	–	–	17/248 (6.9)	–
95% CI			1.1– 5.0				4.3–10.7	
P value versus enoxaparin			<0.001[d] 0.0157[e]					
TKR								
Phase IIb/STARS J-1[68] n/N (%)	26/88 (29.5)	24/92 (26.1)	11/88 (12.5)	8/88 (9.1)	–	–	–	43/89 (48.3)
95% CI	20.0–39.1	17.1–35.1	5.6–19.4	3.1–15.1				37.9–58.7
P value versus placebo	0.01	0.002	<0.001	<0.001				
Phase III/STARS E-3[71] n/N (%)	–	–	22/299 (7.4)	–	–	–	41/295 (13.9)	–
P value versus enoxaparin			<0.001[d] 0.010[e]					
HFS								
Phase III/STARS J-4[72] n/N (%)	–	–	3/46 (6.5)	–	–	–	1/27 (3.7)	–
95% CI			2.2–17.5				0.7–18.3	

Notes: [a]Doses of edoxaban were given orally once daily; [b]Regimen of subcutaneous dalteparin involved an initial dose of 2500 IU followed by 5000 IU once daily thereafter; [c]Subcutaneous enoxaparin 2000 IU equivalent to 20 mg was administered twice daily; [d]Noninferiority, FM test (significance level, one-sided $P < 0.025$); [e]Superiority, FM test (significance level, two-sided $P < 0.05$).

Abbreviations: THR, total hip replacement; TKR, total knee replacement; HFS, hip fracture surgery; CI, confidence interval.

the edoxaban 15 mg, 30 mg, 60 mg, 90 mg, and dalteparin groups, respectively. The incidence of bleeding outcome events was low and similar across the groups. The point estimates for bleeding outcomes were higher in the edoxaban groups than for dalteparin, but statistically significant differences were not detected. An edoxaban dose-response relationship for bleeding outcomes was not identified. This study showed effectiveness of edoxaban administered orally once daily for preventing deep vein thrombosis after total hip replacement.

Phase IIb studies for preventing venous thromboembolism after total knee/hip replacement

A dose-ranging parallel-group, double-blind, placebo-controlled, multicenter Phase IIb study (STARS J-1, NCT01203072, http://www.clinicaltrials.gov) compared edoxaban with placebo for the prevention of deep vein thrombosis in patients undergoing elective total knee replacement in Japan (Table 1).[68] Patients were randomized to receive one of four doses (5, 15, 30 or 60 mg) of edoxaban or placebo orally once daily for 11–14 days. Treatment was started 6–24 hours after surgery. Mechanical thromboprophylaxis, including intermittent pneumatic compression or a venous foot pump, was permitted at the investigator's discretion. The primary efficacy endpoint was the incidence of total deep vein thrombosis, including distal deep vein thrombosis by standardized mandatory bilateral ascending venography, symptomatic pulmonary embolism confirmed by pulmonary scintigraphy, pulmonary arteriography, computed tomography, or symptomatic deep vein thrombosis confirmed before venography. Venography was performed within 24 hours after the end of the study treatment, or within 96 hours if it could not be performed within 24 hours for any reason. The primary safety endpoint was the incidence of major and clinically relevant nonmajor bleeding. A total of

Table 3 Incidence of composite of major and clinically relevant nonmajor bleeding in Phase IIb and III studies of edoxaban for the prevention of venous thromboembolism after major orthopedic surgery

Indication phase/trial	Edoxaban[a]					Dalteparin[b]	Enoxaparin[c]	Placebo
	5 mg	15 mg	30 mg	60 mg	90 mg			
THR								
Phase IIb/No name[67] n/N (%)	–	3/192 (1.6)	3/170 (1.8)	4/185 (2.2)	4/177 (2.3)	0/172 (0.0)	–	–
95% CI		0.3–4.5	0.4– 5.1	0.6–5.4	0.6–5.7	0.0–2.1		
Phase IIb/STARS J-2[69] n/N (%)	–	2/89 (2.2)	1/85 (1.2)	–	–	–	2/87 (2.3)	–
Phase III/STARS J-5[70] n/N (%)	–	–	8/303 (2.6)	–	–	–	11/301 (3.7)	–
P value versus enoxaparin			0.475					
TKR								
Phase IIb/STARS J-1[68] n/N (%)	2/103 (1.9)	4/106 (3.8)	4/103 (3.9)	5/106 (4.7)	–	–	–	4/102 (3.9)
P value versus placebo	0.445	1.000	1.000	1.000				
Phase III/STARS E-3[71] n/N (%)	–	–	22/354 (6.2)	–	–	–	13/349 (3.7)	–
P value versus enoxaparin			0.129					
HFS								
Phase III/STARS J-4[72] n/N (%)	–	–	2/59 (3.4)	–	–	–	2/29 (6.9)	–
95% CI			0.9–11.5				1.9–22.0	

Notes: [a]Doses of edoxaban were given orally once daily; [b]Regimen of subcutaneous dalteparin involved an initial dose of 2500 IU followed by 5000 IU once daily thereafter; [c]Subcutaneous enoxaparin 2000 IU, equivalent to 20 mg was administered.

Abbreviations: THR, total hip replacement; TKR, total knee replacement; HFS, hip fracture surgery; CI, confidence interval.

523 patients were enrolled. Of these, 520 patients received at least one dose of the study treatment and 492 patients completed the study. The final distribution among the treatment groups was 88, 92, 88, 88, and 89 patients in the edoxaban 5 mg, 15 mg, 30 mg, 60 mg, and placebo groups, respectively. The incidence of the primary efficacy endpoint was 29.5%, 26.1%, 12.5%, 9.1%, and 48.3% in the edoxaban 5 mg, 15 mg, 30 mg, 60 mg, and placebo groups, respectively (Table 2). Symptomatic deep vein thrombosis was detected in one patient in the edoxaban 5 mg group, although there were no deep vein thrombosis-related deaths or symptomatic pulmonary embolism. Proximal deep vein thrombosis occurred in one patient each in the 30 mg and 60 mg groups compared with four patients in the placebo group. With regard to mechanical thromboprophylaxis, 21%–28% of patients received intermittent pneumatic compression and 58%–60% of patients received a venous foot pump. For the total study cohort, deep vein thrombosis was observed in 25.0% of users versus 25.6% of nonusers. The incidence of deep vein thrombosis in the placebo group was 47.0% versus 52.2% for users versus nonusers, respectively. The incidence of deep vein thrombosis was similar for users and nonusers of intermittent pneumatic compression or a venous foot pump. The incidence of thromboembolic events was inversely related to edoxaban dose. Paired comparison demonstrated no significant differences in the incidence of thromboembolic events between the 5 mg and 15 mg groups or between the 30 mg and 60 mg groups, but significant differences were shown between the 5 mg or 15 mg groups versus the 30 mg or 60 mg groups. The incidence of composite of major bleeding and clinically relevant nonmajor bleeding was 1.9%, 3.8%, 3.9%, 4.7%, and 3.9% in the edoxaban 5 mg, 15 mg, 30 mg, 60 mg, and placebo groups, respectively (Table 3). There was one occurrence of major bleeding in the edoxaban 60 mg group, although there were no occurrences of major bleeding in other groups. There was no relationship between the incidence of composite of major and clinically relevant bleeding and edoxaban dosage. There was no difference between any of the edoxaban groups or the placebo group in the composite endpoint of bleeding. The incidence of all treatment-related bleeding events, including major, clinically relevant nonmajor, or minor bleeding, was 5.8%, 10.4%, 10.7%, 17.0%, and 17.0% in the edoxaban 5 mg, 15 mg, 30 mg, 60 mg, and placebo groups, respectively. The incidence

increased significantly with increasing edoxaban dose and was significantly higher in the edoxaban 60 mg than in the placebo group. The STARS J-1 trial demonstrated that edoxaban administered orally once daily reduced postoperative deep vein thrombosis in patients undergoing elective total knee replacement in a dose-dependent manner, with no associated increase in major or clinically relevant nonmajor bleeding across the dose range relative to placebo, although all bleeding events increased with dose.

The efficacy, safety, and appropriate dosage regimen of edoxaban for prevention of deep vein thrombosis was evaluated in a randomized, parallel-group, double-blind, open-label, enoxaparin-controlled, multidose, multicenter Phase IIb study (STARS J-2, NCT01203098, http://www.clinicaltrials.gov) in 264 patients undergoing elective unilateral total hip replacement in Japan and Taiwan (Table 1).[69] Double-blind edoxaban 15 mg or 30 mg once daily or open-label subcutaneous enoxaparin 20 mg twice daily was administered for 11–14 days. Edoxaban was started within 6–24 hours and enoxaparin was started within 24–36 hours of surgery. Bilateral venography was performed at the end of the study and centrally adjudicated. The incidence of thromboembolic events was 3.8%, 2.8%, and 4.1% in the edoxaban 15 mg, edoxaban 30 mg, and enoxaparin groups, respectively (Table 2). Thromboembolic events were all asymptomatic distal deep vein thrombosis. The incidence of major and clinically relevant nonmajor bleeding was 2.2%, 1.2%, 2.3% in the edoxaban 15 mg, edoxaban 30 mg, and enoxaparin groups, respectively (Table 3). There was one major bleeding event in the edoxaban 30 mg group classified as clinically overt bleeding accompanied by a decrease in hemoglobin of >2 g/dL. The incidence of adverse drug reactions was 18.0%, 25.9%, 52.9% in the edoxaban 15 mg, edoxaban 30 mg, and enoxaparin groups, respectively. This trial demonstrated that oral administration of edoxaban 15 mg and 30 mg provided efficacy potentially similar to that of enoxaparin for the prevention of thromboembolic events in patients undergoing total hip replacement. The incidence of major and clinically relevant nonmajor bleeding was comparable with that of enoxaparin.

Phase III study in elective total hip replacement

In the Phase III STARS J-5 trial (NCT01181167 http://www.clinicaltrials.gov), edoxaban showed efficacy superior to that of enoxaparin in the prevention of deep vein thrombosis events in 610 patients following total hip replacement (Table 1).[70] STARS J-5 was a randomized, parallel-group, double-blind, double-dummy, enoxaparin-controlled, noninferiority, multicenter study in Japan. Patients were randomized to receive oral edoxaban 30 mg once daily or subcutaneous enoxaparin 2000 IU (equivalent to 20 mg), twice daily for 11–14 days. Edoxaban was initiated 6–24 hours after surgery, and enoxaparin was initiated 24–36 hours after surgery, which is the Japanese standard of care. The primary efficacy endpoint was the composite of symptomatic and asymptomatic deep vein thrombosis and pulmonary embolism. The primary safety endpoint was the incidence of major bleeding and clinically relevant nonmajor bleeding events. The incidence of any deep vein thrombosis was 2.4% in the edoxaban group and 6.9% in the enoxaparin group (relative risk reduction 65.7%; absolute risk difference –4.5%, 95% confidence interval –8.6% to –0.9%; $P < 0.001$ for noninferiority; $P = 0.0157$ for superiority, Table 2). The deep vein thromboses were all asymptomatic. The incidence of proximal deep vein thrombosis was 0.4% in the edoxaban group and 0.8% in the enoxaparin group. The incidence of distal deep vein thrombosis was 2.4% in the edoxaban group and 6.5% in the enoxaparin group. No symptomatic deep vein thrombosis or pulmonary embolism was observed in either treatment group. The incidence of major and clinically relevant nonmajor bleeding events was 2.6% in the edoxaban group and 3.7% in the enoxaparin group ($P = 0.475$, Table 3). Major bleeding occurred in 0.7% of the edoxaban group and 2.0% of the enoxaparin group. The rate of elevated serum aminotransferase levels of more than three times the upper limit of normal was 2.6% with edoxaban and 10% with enoxaparin. The STARS J-5 trial demonstrated that oral edoxaban 30 mg once daily had efficacy superior to that of enoxaparin 20 mg twice daily for the prevention of thromboembolic events following total hip replacement and was associated with a similar incidence of major and clinically relevant nonmajor bleeding events.

Phase III study in elective total knee replacement

STARS E-3 (NCT NCT01181102) was a randomized, parallel-group, double-blind, double-dummy, enoxaparin-controlled, noninferiority, multicenter Phase III study of thromboprophylaxis in 716 Japanese patients undergoing total knee replacement (Table 1).[71] Patients were randomized to receive oral edoxaban or subcutaneous enoxaparin. The treatment regimen and primary efficacy outcome were the same as those in the Phase III STARS J-5 trial for elective total hip replacement. The incidence of any deep vein thrombosis was 7.4% in the edoxaban group and 13.9% in the

enoxaparin group (relative risk reduction 46.8%; $P < 0.001$ for noninferiority; $P = 0.010$ for superiority, Table 2). No pulmonary embolism was observed in either treatment group. The incidence of major and clinically relevant nonmajor bleeding events was 6.2% in the edoxaban group and 3.7% in the enoxaparin group ($P = 0.129$, Table 3). The rate of elevated serum aminotransferase levels of more than three times the upper limit of normal was 1.4% with edoxaban and 8.0% with enoxaparin. The STARS E-3 trial demonstrated that oral edoxaban 30 mg once daily had efficacy superior to that of subcutaneous enoxaparin 20 mg twice daily in the prevention of thromboembolic events following total knee replacement.

Phase III study in hip fracture surgery

The efficacy of edoxaban in the treatment of deep vein thrombosis in 92 patients undergoing hip fracture (femoral neck, trochanteric, and subtrochanteric) surgery has been evaluated in the randomized, open-label, enoxaparin-controlled, multicenter Phase III STARS J-4 trial (NCT01181141) in Japan.[72] Patients were randomized in a 2:1 ratio to an edoxaban group or an enoxaparin group (Table 1). The treatment regimen was the same as that of the other Phase III studies (STARS J-5 for elective total hip replacement and STARS E-3 for elective total knee replacement). Venography of both legs was conducted within 24 hours of the last dose of the study medication. Seventy-six of 92 patients enrolled completed the study. Baseline characteristics were similar between the treatment groups, although creatinine clearance was lower in the edoxaban group than in the enoxaparin group. The incidence of thromboembolic events was 6.5% in the edoxaban group and 3.7% in the enoxaparin group (Table 2). All thromboembolic events were asymptomatic distal deep vein thrombosis. The incidence of major and clinically relevant nonmajor bleeding was 3.4% in the edoxaban group and 6.9% in the enoxaparin group (Table 3). There was one patient with major bleeding in each group. The incidence of adverse events was similar between the treatment groups. The STARS J-4 trial demonstrated that oral edoxaban 30 mg once daily had similar safety and efficacy to that of subcutaneous enoxaparin for the prevention of deep vein thrombosis in patients undergoing hip fracture surgery.

Pooled analysis of phase III studies

The results of a pooled analysis of Phase III studies for total hip replacement (STARS J-5[29]) and total knee replacement (STARS E-3[30]) comprising a total of 1326 Japanese and Taiwanese patients were presented at the 53rd Annual Meeting of the American Society of Hematology in December 2011.[73] The objective of this pooled analysis was to investigate the effects of edoxaban on deep vein thrombosis and bleeding in key patient subgroups. Patients were randomized to receive oral edoxaban 30 mg once daily or subcutaneous enoxaparin 2000 IU (equivalent to 20 mg) twice daily for 11–14 days. Edoxaban was initiated 6–24 hours and enoxaparin 24–36 hours postoperatively, which is the standard of care in Japan. The primary efficacy outcome was the composite of symptomatic and asymptomatic deep vein thrombosis and pulmonary embolism. The principal safety outcome was the incidence of major and clinically relevant nonmajor bleeding. A total of 1307 patients received at least one dose of edoxaban or enoxaparin. Over 70% of patients received physiotherapy, including intermittent pneumatic compression and/or elastic stockings. Overall, edoxaban significantly reduced the incidence of the composite of symptomatic and asymptomatic deep vein thrombosis and pulmonary embolism compared with enoxaparin (5.1% versus 10.7%, $P < 0.001$). Subgroup analysis showed that edoxaban numerically reduced the incidence of the composite efficacy endpoint regardless of age or body weight. The effect was statistically significant in patients < 75 years of age and in those weighing < 70 kg. Edoxaban was also significantly more effective than enoxaparin in the presence or absence of concomitant physiotherapy. The incidence of major and clinically relevant nonmajor bleeding events was 4.6% versus 3.7% in the edoxaban and enoxaparin groups, respectively ($P = 0.427$). Subgroup analysis of major and clinically relevant nonmajor bleeding indicated no significant difference between edoxaban and enoxaparin in any of the patient subgroups evaluated, based on age, weight, or creatinine clearance. Therefore, edoxaban 30 mg once daily is superior to enoxaparin 20 mg twice daily in the prevention of deep vein thrombosis events following total hip replacement and total knee replacement without a statistically significant increase in bleeding in important patient subgroups likely to receive this treatment.

Discussion

Clinical trials suggest that edoxaban is at least as effective as enoxaparin and has a risk of major bleeding similar to that of enoxaparin for the prevention of deep vein thrombosis in patients undergoing major orthopedic surgery. Factor Xa inhibition has emerged as an attractive therapeutic target for reducing the risk of deep vein thrombosis. New oral factor

Xa inhibitors are an emerging class of oral anticoagulants with potential benefits over warfarin. Edoxaban is a novel direct factor Xa inhibitor that has undergone Phase III clinical trials in deep vein thrombosis prophylaxis after major orthopedic surgery.[70–72] Edoxaban is rapidly absorbed, with a time to peak plasma concentration of 1–2 hours and a short half-life of 5.8–10.7 hours.[62] Edoxaban inhibits factor Xa activity directly and selectively.[56,57] Edoxaban has strong antithrombotic properties as a result of factor Xa inhibition.[56,57,60,61] Coagulation monitoring is not required for edoxaban because of its predictable linear pharmacokinetic and pharmacodynamic profile, lack of an effect of food, and low plasma protein binding.[62,63] In Phase II and III clinical trials, oral administration of edoxaban showed efficacy superior to that of subcutaneously administered dalteparin or enoxaparin in the prevention of thromboembolic events, with similar safety following major orthopedic surgery.

Edoxaban has shown promising results for preventing deep vein thrombosis after major orthopedic surgery. Edoxaban is approved for the prevention of deep vein thrombosis in patients undergoing major orthopedic surgery by a government agency only in Japan at present. Edoxaban has the potential to become a first choice drug in preventing deep vein thrombosis after major orthopedic surgery. In the Phase II and III clinical studies, the efficacy and safety of edoxaban were compared with that of the low molecular weight heparins, dalteparin or enoxaparin.[67,69–72] However, the dose should be adjusted in patients with renal impairment, low body weight, and/or older age.[74] In Japan, edoxaban is contraindicated in patients whose creatinine clearance is $<$30 mL/minute.[74] Subgroup analysis of pooled data from clinical trials in patients undergoing major orthopedic surgery in Japan and Taiwan revealed a higher bleeding risk in an oral edoxaban 30 mg once daily subgroup with moderate renal impairment (creatinine clearance 30–50 mL/minute), body weight $<$ 50 kg, and/or age $\geq$ 75 years, for whom a daily dose of 15 mg is recommended.[74] Furthermore, P-glycoprotein inhibitors, such as quinidine sulfate, verapamil hydrochloride, amiodarone hydrochloride, erythromycin, and itraconazole, are expected to increase the bioavailability of edoxaban by inhibition of P-glycoprotein in the intestine. Coadministration of these drugs could increase plasma levels of edoxaban, leading to an increased bleeding risk.[56,74,75] Therefore, a reduced dosage should be considered when patients are receiving concomitant administration of these drugs.[74]

The incidence of total deep vein thrombosis in the multinational Phase IIb study of total hip replacement[67] was higher than that in the Phase IIb trial in Japan[69] and Taiwan and in the Phase III trial in Japan.[70] The incidence might be affected by ethnicity, body mass index, or body weight. The great majority (98%) of patients in the multinational trial were Caucasian. The incidence of deep vein thrombosis in the general population is lower among Japanese and Taiwanese than in Caucasians.[76,77] Average body mass index in the multinational Phase IIb trial was approximately 28 kg/m^2, while average body weight in the Phase III trial in Japan was 57.4 kg. It is presumed that patients in the multinational trial were heavier than those in the Japanese trial. Body mass index has a stronger association with risk of deep vein thrombosis not only in the general population[78,79] but also in patients after total hip arthroplasty.[80,81]

Mechanical thromboprophylaxis with a venous foot pump or intermittent pneumatic compression is recommended with/without anticoagulant thromboprophylaxis for patients undergoing major orthopedic surgery according to guidelines from the American College of Chest Physicians, National Institute for Health and Clinical Excellence, and American Association of Orthopedic Surgeons.[1,4,42] Mechanical thromboprophylaxis with intermittent pneumatic compression has been used for almost 25 years.[82] Mechanical prophylaxis with intermittent pneumatic compression in combination with other nonpharmacologic modalities, such as regional anesthesia and rapid mobilization, with or without aspirin, is also reportedly as being effective as thromboprophylaxis for deep vein thrombosis.[82–88] Among the reviewed articles, only a multidose Phase IIb report for patients undergoing total knee replacement[68] has described the results of mechanical prophylaxis. The incidence of deep vein thrombosis was similar for users and nonusers of intermittent pneumatic compression or a venous foot pump in the trial.

Limitations

Some limitations of past clinical studies of edoxaban for deep vein thrombosis prophylaxis after major orthopedic surgery should be noted. First, the racial and ethnic distribution of the patient populations in these studies was disproportionate. Although the dose-finding Phase IIb trial was multinational, more than 75% of patients were recruited from Russia and Ukraine, and only about 17% were recruited from the US, with less than 0.5% from Western Europe. Patients in the other Phase II and III trials were only recruited from Japan or Taiwan. Second, the scale of all studies was small. The largest one, which was a dose-finding Phase IIb trial for total hip replacement, included only 903 patients, and the patient population in the pooled analysis of Phase III studies was

only 1326. Third, treatment with enoxaparin 20 mg twice daily was started within 24–36 hours of surgery. This regimen is the standard of care in Japan but is not commonly used in other countries. Consequently, larger multinational trials, in which the protocol of comparator treatment is popular in other regions, are required to confirm the efficacy and safety as well as optimum dose of edoxaban for the prevention of deep vein thrombosis after major orthopedic surgery. There are some reports comparing the efficacy and safety of the indirect factor Xa inhibitor, fondaparinux, with that of enoxaparin for the prevention of deep vein thrombosis after major orthopedic surgery.[89–93] However, no clinical results for the efficacy and safety of the factor Xa inhibitors has ever been reported. Furthermore, specific antidotes are still being investigated.[94] It is expected that more information will be reported in the near future.

Disclosure

The authors report no conflicts of interest in this work.

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