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Edoxaban Plus Aspirin vs Dual Antiplatelet Therapy in Endovascular Treatment of Patients With Peripheral Artery Disease: Results of the ePAD Trial

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Abstract

Purpose: To report a randomized study that investigated the safety (risk of major bleeds) and potential efficacy of edoxaban, an oral anticoagulant that targets the major components of arterial thrombi, to prevent loss of patency following endovascular treatment (EVT). **Methods:** Between February 2012 and June 2014, 203 patients who underwent femoropopliteal EVT were randomized to receive aspirin plus edoxaban or aspirin plus clopidogrel for 3 months in the Edoxaban in Peripheral Arterial Disease (ePAD) study (*ClinicalTrials.gov* identifier NCT01802775). Randomization assigned 101 patients (mean age 68.0±10.4 years; 67 men) to the edoxaban group and 102 patients (mean age 66.7±8.6 years; 78 men) to the clopidogrel group. The primary safety endpoint was bleeding as classified by the TIMI (Thrombolysis in Myocardial Infarction) criteria and ISTH (International Society of Thrombosis and Hemostasis) criteria; the efficacy endpoint was the rate of restenosis/reocclusion. **Results:** There were no major or life-threatening bleeding events in the edoxaban group, while there were 2 major and 2 life-threatening bleeding events in the clopidogrel group by the TIMI criteria. By the ISTH classification, there was 1 major and 1 life-threatening bleeding event vs 5 major and 2 life-threatening bleeding events, respectively [relative risk (RR) 0.20, 95% confidence interval (CI) 0.02 to 1.70]. The bleeding risk was not statistically different with either treatment when assessed by TIMI or ISTH. Following 6 months of observation, there was a lower incidence of restenosis/reocclusion with edoxaban compared with clopidogrel (30.9% vs 34.7%; RR 0.89, 95% CI 0.59 to 1.34, p=0.643). **Conclusion:** These results suggest that patients who have undergone EVT have similar risks for major and life-threatening bleeding events with edoxaban and aspirin compared with clopidogrel and aspirin. The incidence of restenosis/reocclusion events, while not statistically different, was lower with edoxaban and aspirin, but an adequately sized trial will be needed to confirm these findings.

Keywords

antiplatelet therapy, aspirin, bleeding, clopidogrel, endovascular treatment, edoxaban, femoropopliteal segment, patency, peripheral artery disease, reocclusion, restenosis

Introduction

In contrast to percutaneous coronary intervention (PCI), evidence for medical therapy following peripheral endovascular treatment (EVT) from randomized controlled studies is sparse. Consequently, medical management of patients with peripheral artery disease (PAD) who have undergone EVT is not evidence-based but extrapolated from the PCI literature. Pharmacological management after EVT is based on guideline recommendations and varies from aspirin only to dual antiplatelet therapy (DAPT; clopidogrel + aspirin) for 1 to 3 months followed by long-term use of aspirin; these recommendations are controversial.[1-3]

Restenosis rates following EVT in the femoropopliteal region with conventional treatment (DAPT) range from 17% to more than 40% and increase with longer lesion length.[4-8] Compared with PCI, these rates are disappointingly high, frustrating for the patients, vexing for the interventionists, and

economically burdensome for society. Restenosis and loss of patency following EVT is largely a consequence of catheter-induced damage to the endothelium resulting in the eventual activation of both platelets and coagulation factors.[9,10]

Attempts have been made in the past to target both platelets and fibrin with limited or no success; treatment with 2500 units of dalteparin given subcutaneously for 3 months after femoropopliteal angioplasty failed to reduce restenosis/reocclusion at 12 months.[11] Additionally, the Warfarin Antiplatelet Vascular Evaluation (WAVE) trial conducted in patients with stable PAD demonstrated an increased risk of bleeding without increased benefit regarding ischemic events using a regimen that combined an antiplatelet (aspirin, ticlopidine, or clopidogrel) and oral anticoagulant (OAC; warfarin or acenocoumarol) compared with antiplatelet alone.[12]

Progress in targeting both platelet and fibrin was impeded due, in part, to the inconvenience associated with the use of OACs and concern for an excessive risk of bleeding.[13,14] However, non–vitamin K antagonist OACs (NOACs) offer reliable levels of anticoagulation and lower rates of intracranial hemorrhage and life-threatening or fatal bleeding compared with vitamin K antagonists,[15-17] along with a greater convenience of use. Therefore, it is now more feasible to conduct clinical studies with regimens that address the major components of the thrombus without concern for monitoring and perhaps more acceptable risk of bleeding.

With this background, a proof-of-concept study was devised to test the combined use of a direct factor Xa inhibitor NOAC (edoxaban) and the mainstay antiplatelet therapy (aspirin) vs conventional treatment using DAPT (clopidogrel and aspirin). The aim was to observe safety with regard to bleeding and potential efficacy with regard to maintenance of vessel patency in PAD patients following femoropopliteal EVT. To our knowledge, no other study has used a NOAC in a dual antithrombotic regimen in the PAD setting.

Methods

Study Design

The edoxaban in patients with PAD (ePAD) study was a prospective, randomized, open-label, blinded-endpoint proof-of-concept trial involving 40 sites from Europe, Israel, and the United States. The study was registered on the National Institutes of Health website (*ClinicalTrials.gov*; identifier NCT01802775). Health authorities in every country in which the study was conducted reviewed and approved the study protocol and subsequent amendments prior to initiation of the study. Similarly, respective ethics committees and institutional review boards reviewed and approved the protocol. The details of the design and a full list of inclusion and exclusion criteria have been previously published.[18] In brief, eligible patients were those with symptomatic PAD (Rutherford categories 2–5) who underwent successful EVT (residual stenosis ≤30%[19]) of the superficial femoral or above-knee popliteal arteries. At least 1 patent runoff vessel to the foot was required, and this could be achieved with additional EVT during the index intervention. Major exclusion criteria included severe renal impairment defined as creatinine clearance (CrCl) <30 mL/min, active bleeding or known high risk for bleeding, and an ongoing other indication for DAPT or anticoagulant treatment. All patients provided written informed consent to participate.

The Steering Committee was composed of academic investigators and representatives of Daiichi Sankyo, the study sponsor. Data and safety oversight was provided by an independent Data Monitoring Committee made up of academic physicians/scientists not associated with the study sponsor. Blinded adjudication of bleeding and clinical events was carried out by a Clinical Events Committee comprised of experts located at University Medical Center Utrecht (the Netherlands). The efficacy endpoints were acquired by duplex ultrasonography and read independently by experts at the core laboratory (VasCore; Massachusetts General Hospital, Boston, MA, USA) who were blinded to the treatment assignment. Study data were collected, managed, and analyzed by Medpace, Inc (Cincinnati, OH, USA). The steering committee members and 2 additional study site investigators formed the writing group and contributed to iterative drafting, review, and subsequent finalization of the manuscript. All authors assure completeness and accuracy of the data and the conformity of the study protocol.

Randomization and Treatment Protocol

After successful EVT, patients were randomized within 4 hours of hemostasis to receive either edoxaban (60 mg/d) in

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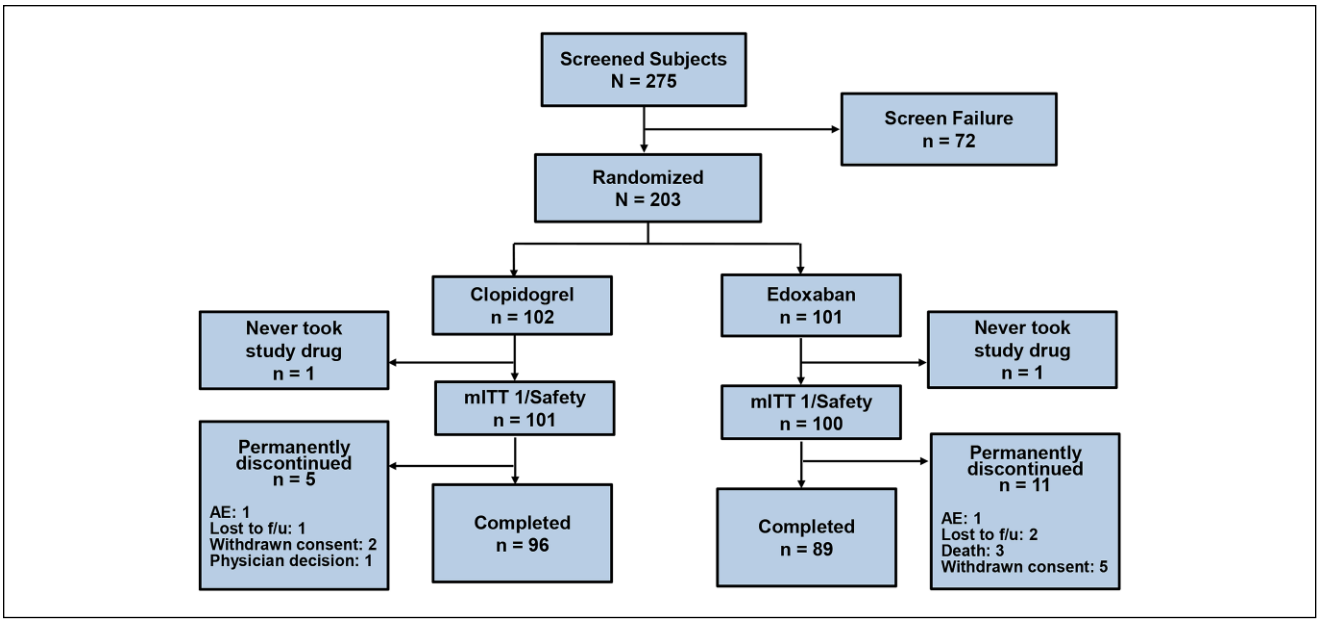

Figure 1. Diagram of patient flow and treatment to 6 months for the modified intent-to-treat (mITT) set including all randomized subjects who received at least 1 dose of the study drug. AE, adverse event; f/u, follow-up.

conjunction with aspirin (100 mg/d) or clopidogrel (a 300-mg mg loading dose followed by 75 mg/d) and aspirin (100 mg/d) for 3 months. Treatment group allocation was 1:1 via a 24-hour interactive computer response system. For patients randomized to the edoxaban group, the dose was reduced by 50% (30 mg) if the patients had low body weight (≤60 kg), moderate renal impairment (CrCl ≥30 mL/min and ≤50 mL/min Cockcroft-Gault formula), and/or concomitant use of select P-glycoprotein inhibitors (verapamil, quinidine, or dronedarone) at the time of randomization or intercurrently during the 3 months of active treatment. Patients in both treatment arms continued on aspirin (100 mg/d) for ≥6 months. Follow-up assessments were required at 1, 2, 3, 4, and 6 months following randomization, during which endpoints and drug compliance measures were ascertained.

Patient Population

Between February 2012 and June 2014, 275 symptomatic PAD patients (Rutherford category 2–5) were screened for eligibility to participate in the study; of these, 72 did not meet criteria for inclusion. Of the 203 patients who met eligibility criteria and had successful EVT, 101 patients (mean age 68.0±10.4 years; 67 men) were randomized to edoxaban and 102 (mean age 66.7±8.6 years; 78 men) were assigned to clopidogrel as illustrated in Figure 1. One patient in each group did not take any study drug. Baseline patient characteristics are presented in Table 1.

Endpoints

The primary study endpoint was safety with regard to bleeding as assessed by blinded adjudication using both the International Society on Thrombosis and Hemostasis (ISTH) criteria and the Thrombolysis in Myocardial Infarction (TIMI) criteria for bleeding.[20,21] The efficacy endpoint was restenosis or reocclusion at 6 months, defined by a peak systolic velocity ratio (PSVR) ≥2.4 measured at the treated segment using duplex ultrasonography[19] and read centrally without awareness of treatment assignment.

Other endpoints of interest were deterioration in extremity hemodynamics assessed by the ankle-brachial index (ABI), Rutherford category of ischemia, symptomatic acute thrombosis, target lesion revascularization (TLR; percutaneous or surgical), amputation, myocardial infarction (MI), systemic embolic events, cardiovascular death, all-cause mortality, and major adverse cardiovascular events (MACEs; nonfatal MI, nonfatal stroke, and cardiovascular death).

Statistical Analysis

Assuming a 6% incidence of major and clinically relevant nonmajor (CRNM) bleeding in both groups, 100 subjects in each treatment group would provide a 95% confidence interval (CI) within 6.6% of the point estimate, which was considered adequate precision to estimate bleeding event rates in this proof-of-concept study. All safety analyses were performed using the safety analysis set, which included all patients who underwent randomization and received at least 1 dose of the study drug. Bleeding events during the 3-month on-treatment period were adjudicated and compared using a normal approximation to the binomial distribution. Time-to-event curves were calculated using the Kaplan-Meier method.

A modified intent-to-treat (mITT) analysis, including all randomized subjects who received at least 1 dose of the

Table 1. Demographics of All Patients Randomized in the Study.[a]

Variable	Clopidogrel (n=102)	Edoxaban (n=101)
Age, y	66.7±8.6	68.0±10.4
≥65	69 (67.6)	71 (70.3)
≥75	16 (15.7)	23 (22.8)
Women	24 (23.5)	34 (33.7)
Race		
White	95 (93.1)	94 (93.1)
Not Hispanic or Latino	84 (90.3)	79 (89.8)
Height, cm	171.4±9.0	170.0±9.2
Weight, kg	81.9±17.2	78.6±15.4
Body mass index, kg/m^2	27.7±4.9	27.1±4.6
Low body weight (≤60 kg)	10 (9.8)	11 (10.9)
Diabetes	40 (39.2)	41 (40.6)
HbA1c, %	8.1±1.8	7.9±1.8
Smoking		
Never	10 (9.8)	19 (18.8)
Current	36 (35.3)	35 (34.7)
Former	56 (54.9)	47 (46.5)
Alcohol use		
None or rarely	62 (60.8)	58 (57.4)
Currently consumes	40 (39.2)	43 (42.6)
Moderate renal impairment[b]	15 (14.7)	19 (18.8)
Baseline CrCl, mg/dL		
≤50	6/97 (6.2)	12/97 (12.4)
>50 and <80	23/97 (23.7)	30/97 (30.9)
≥80	68/97 (70.1)	55/97 (56.7)
>95	43/97 (44.3)	37/97 (38.1)
P-glycoprotein inhibitor use at randomization	1 (1.0)	3 (3.0)
Dose adjustment status at randomization	22 (21.6)	23 (22.8)
Country		
United States	47 (46.1)	42 (41.6)
Austria	13 (12.7)	15 (14.9)
Belgium	6 (5.9)	9 (8.9)
Germany	11 (10.8)	10 (9.9)
Netherlands	5 (4.9)	8 (7.9)
Switzerland	13 (12.7)	12 (11.9)
Israel	7 (6.9)	5 (5.0)
Hypertension	85 (83.3)	83 (82.2)
Cholesterol, mmol/L	4.3±1.4 (n=97)	4.4±1.0 (n=96)
HDL cholesterol, mmol/L	1.2±0.3 (n=97)	0.3±0.4 (n=96)
LDL cholesterol, mmol/L	2.5±1.2 (n=95)	2.6±0.9 (n=95)
Triglycerides, mmol/L	1.3±1.1 (n=97)	1.3±0.8 (n=96)

Abbreviations: CrCl, creatinine clearance; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density cholesterol.
[a]Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage). Percentages were based on the number of subjects in the column heading as the denominator unless specified otherwise.
[b]Creatinine clearance ≥30 to ≤50 mL/min.

study drug and had at least 1 duplex scan, was conducted for the primary efficacy measure and other clinical outcome events. The primary analysis included all efficacy measures from randomization through the end-of-study visit, regardless of the duration of the subject's study treatment. The proportion of patients with restenosis or reocclusion was summarized for each treatment group. The difference and relative risk (RR) between treatment groups were calculated using the normal approximation to binomial distribution, as well as a logistic regression model adjusting for treatment, dose adjustment status at randomization, and stent placement.

Table 2. Baseline Disease Characteristics and Procedure Details of All Patients Randomized in the Study.[a]

Variable	Clopidogrel (n=102)	Edoxaban (n=101)
Rutherford category		
2	30 (29.4)	29 (28.7)
3	56 (54.9)	59 (58.4)
4	11 (10.8)	5 (5.0)
5	5 (4.9)	8 (7.9)
Runoff vessels (<50% stenosis)		
1	24/102 (23.5)	22/100 (22.0)
2	34/102 (33.3)	40/100 (40.0)
3	44/102 (43.1)	38/100 (38.0)
Lesion location		
SFA	94/102 (92.2)	92/99 (92.9)
Popliteal	8/102 (7.8)	7/99 (7.1)
Lesion length, cm	12.0±10.0 (n=102)	12.5±10.1 (n=100)
Lesion severity		
Stenosis	66/102 (64.7)	64/100 (64.0)
Occlusion	36/102 (35.3)	36/100 (36.0)
Baseline ABI	0.69±0.27 (n=100)	0.67±0.28 (n=94)
Routinely taking aspirin	90 (88.2)	85 (84.2)
Baseline antithrombotic treatment		
Aspirin	51/102 (50.0)	54/100 (54.0)
Heparin (intravenous)	12/102 (11.8)	11/100 (11.0)
Heparin (subcutaneous)	0/102 (0.0)	1/100 (1.0)
Other	3/102 (2.9)	0/100 (0.0)
None	36/102 (35.3)	34/100 (34.0)
Intraprocedural antithrombotic treatment		
Heparin	94/102 (92.2)	90/100 (90.0)
Other	5/102 (4.9)	7/100 (7.0)
None	3/102 (2.9)	3/100 (3.0)
Treated lesion length, cm	13.5±11.0 (n=102)	14.2±10.6 (n=100)
Residual stenosis, %	6.4±8.8 (n=102)	8.2±9.8 (n=100)
Vessel diameter, mm	5.4±0.8 (n=101)	5.7±1.0 (n=100)
Inflow/outflow lesions treated	31/99 (31.3)	32/100 (32.0)
Inflow/outflow lesions revascularized	30/31 (96.8)	31/32 (96.9)
Stent placement	55/102 (53.9)	53/100 (53.0)
Bare metal	41/102 (40.2)	41/100 (41.0)
Drug-eluting	14/102 (13.7)	12/100 (12.0)
Vascular access site hemostasis	102/102 (100.0)	100/100 (100.0)
Manual compression	57/102 (55.9)	53/100 (53.0)
Closure device	45/102 (44.1)	47/100 (47.0)
Procedure success	102/102 (100.0)	100/100 (100.0)
Distal embolization	8/102 (7.8)	11/100 (11.0)
ABI at 1 month	0.97±0.19 (n=93)	0.93±0.19 (n=93)

Abbreviations: ABI, ankle-brachial index; SFA, superficial femoral artery.
[a]Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage). Percentages were based on the number of subjects in the column heading as the denominator unless specified otherwise.

Results

Study Groups

With a few numerical differences, baseline characteristics were comparable and not significantly different (Table 1). Among patients ≥75 years of age, 22.8% were in the edoxaban group (23/101) compared with 15.7% in the clopidogrel group (16/102). There were more men than women in both treatment groups (66.3% edoxaban and 76.5% clopidogrel, respectively). The duration of PAD was similar in both groups (Table 2). Nearly 86% of the patients were classified in Rutherford categories 2 or 3 (~14% in categories 4 or 5). Mean lesion lengths in both groups were similar (12.5 cm in the edoxaban group vs 12.0 cm in the clopidogrel groups)

Table 3. Treatment Compliance and Adherence in the mITT-1 Safety Set.[a]

Variable	Clopidogrel (n=101)	Edoxaban (n=100)
Time from randomization to first dose, h	1.3±2.2	1.7±2.4
Study drug interrupted	15 (14.9)	27 (27.0)
Study drug permanently discontinued	7 (6.9)	22 (22.0)
Treatment duration, d	86.3±20.7	79.3±28
Total patient-years	23.9	21.7

Abbreviations: mITT, modified intention-to-treat set including all randomized subjects who received at least 1 dose of the study drug.
[a]Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage).

Table 4. Adjudicated Bleeding Events in the On-Treatment Period for the mITT-1 Safety Set.

Bleeding	Clopidogrel (n=101)[a]	Edoxaban (n=100)[a]	Treatment Difference, %[b]	Edoxaban/Clopidogrel RR[b]
TIMI criteria including access site bleeding				
Major	2 (2.0) [0.2 to 7.0]	0 (0.0) [—]	—	—
Life-threatening[c]	2 (2.0) [0.2 to 7.0]	0 (0.0) [—]	—	—
Any	9 (8.9) [4.2 to 16.2]	5 (5.0) [1.6 to 11.3]	−3.9 [−10.9 to 3.1]	0.56 [0.19 to 1.62]
TIMI criteria excluding access site bleeding				
Major	2 (2.0) [0.2 to 7.0]	0 (0.0) [—]	—	—
Life-threatening[c]	2 (2.0) [0.2 to 7.0]	0 (0.0) [—]	—	—
Any	7 (6.9) [2.8 to 13.8]	2 (2.0) [0.2 to 7.0]	−4.9 [−10.6 to 0.7]	0.29 [0.06 to 1.36]
ISTH criteria including access site bleeding				
Major/CRNM	8 (7.9) [3.5 to 15.0]	11 (11.0) [5.6 to 18.8]	3.1 [−5.0 to 11.2]	1.39 [0.58 to 3.31]
Major	5 (5.0) [1.6 to 11.2]	1 (1.0) [0.0 to 5.4]	−4.0 [−8.6 to 0.7]	0.20 [0.02 to 1.70]
Life-threatening[c]	2 (2.0) [0.2 to 7.0]	1 (1.0) [0.0 to 5.4]	—	—
Any	28 (27.7) [19.3 to 37.5]	30 (30.0) [21.2 to 40.0]	2.3 [−10.2 to 14.8]	1.08 [0.70 to 1.67]
ISTH criteria including access site bleeding				
Major/CRNM	6 (5.9) [2.2 to 12.5]	6 (6.0) [2.2 to 12.6]	0.1 [−6.5 to 6.6]	1.01 [0.34 to 3.03]
Major	4 (4.0) [1.1 to 9.8]	1 (1.0) [0.0 to 5.4]	—	—
Life-threatening[c]	2 (2.0) [0.2 to 7.0]	1 (1.0) [0.0 to 5.4]	—	—
Any	23 (22.8) [15.0 to 32.2]	25 (25.0) [16.9 to 34.7]	2.2 [−9.6 to 14.0]	1.10 [0.67 to 1.80]

Abbreviations: CI, confidence interval; CRNM, clinically relevant nonmajor; ISTH, International Society of Thrombosis and Hemostasis; mITT, modified intention-to-treat set including all randomized subjects who received at least 1 dose of the study drug; RR, relative risk; TIMI, Thrombolysis in Myocardial Infarction.
[a]Data are presented as the count (percentage) [exact binomial 95% CI].
[b]The 95% CI in brackets is calculated using a normal approximation to the binomial distribution.
[c]Defined as bleeding at an intracranial site or that leads to hemodynamic compromise.

with ranges from 1 to 42 cm. In all, 92% of the index lesions were in the femoral segment and 8% in the popliteal segment. Slightly more patients with moderate renal disease were randomized to the edoxaban group (18.8% vs 14.7%).

Initiation of treatment and compliance with treatment are shown in Table 3. The mean time from randomization to first dose was longer in the edoxaban group (1.7 hours) than in the clopidogrel group (1.3 hours). More patients in the edoxaban group discontinued the study than in the clopidogrel group (11 vs 5) primarily due to withdrawal of consent. In all, 42 patients (27 edoxaban and 15 clopidogrel) interrupted the study drug, of which 29 discontinued treatment permanently (22 edoxaban and 7 clopidogrel). The cumulative patient years of treatment were fewer in the edoxaban group (21.7 years) than in the clopidogrel group (23.9 years).

Safety

The on-treatment bleeding results according to the 2 bleeding classifications used in the study are presented in Table 4. According to the TIMI classification, there were no major or life-threatening bleeding events and 5 bleeding events classified as "any" in the edoxaban group vs 2 major and 2 life-threatening bleeding events along with 9 bleeding events classified as "any" in the clopidogrel group (Figure 2A), but these differences were not statistically significant. Excluding vascular access bleeding events did not significantly change the TIMI bleeding assessment results.

Using the ISTH bleeding classification (Figure 2B), there were 11 major or CRNM bleeds in the edoxaban group vs 8 major or CRNM bleeds in the clopidogrel arm (RR

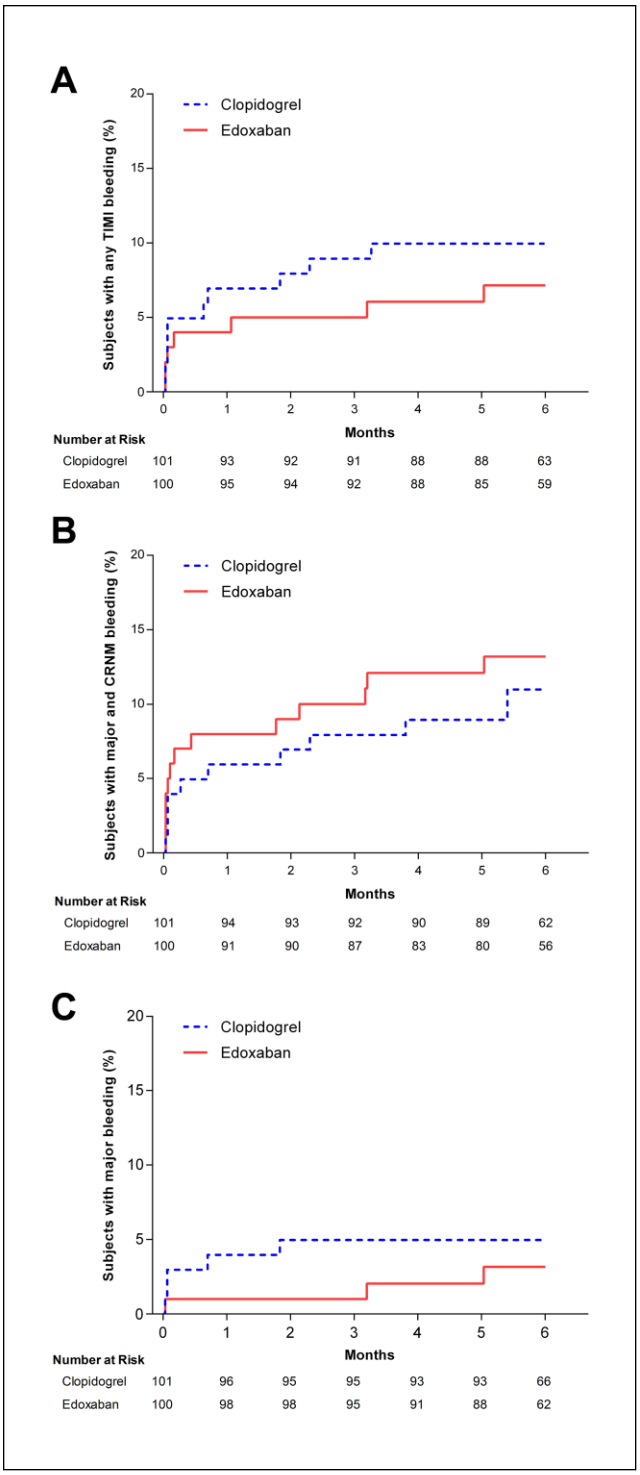

Figure 2. Kaplan-Meier estimates for (A) adjudicated bleeding events per the TIMI (Thrombolysis in Myocardial Infarction) criteria, (B) adjudicated major and clinically relevant nonmajor bleeding (CRNM) events per the ISTH (International Society of Thrombosis and Hemostasis) criteria, and (C) adjudicated major bleeding events per the ISTH criteria. The standard error did not exceed 10% for either treatment group at any time point in any analysis.

1.39, 95% CI 0.58 to 3.31, p=0.481); again, these were not statistically significant. When vascular access site events were excluded there were no differences between the groups in terms of major or CRNM bleeding events (6 vs 6; p>0.99). Comparing major/life-threatening bleeding events only, there were 2 in the edoxaban group compared with 7 in the clopidogrel group (RR 0.20, 95% CI 0.02 to 1.70; Figure 2C). Censoring vascular access bleeding did not significantly change the result. Three patients died during the study, all of which were off treatment and were in the edoxaban group.

Efficacy

Among the patients who had duplex, there were 62 restenosis/reocclusion lesions recorded within 6 months (Table 5); the incidence was lower in the edoxaban group (30.9%) than in the clopidogrel group (34.7%; RR 0.89, 95% CI 0.59 to 1.34, p=0.643; Figure 3A). Additionally, there were 71 first occurrences of the composite of restenosis/reocclusion and TLR endpoint [33.7% in the edoxaban group and 40.2% in the clopidogrel group (RR 0.82, 95% CI 0.53 to 1.18, p=0.373)]. Additional analysis of the composite of restenosis/reocclusion, TLR, and amputation endpoint also showed a lower rate in the edoxaban group than in the clopidogrel group (33.7% vs 41.2%; RR 0.82, 95% CI 0.56 to 1.18, p=0.3). Similarly, when MACEs were included in the composite, the incidence of events in the edoxaban group remained lower (33.7% vs 42.3%; RR 0.80, 95% CI 0.55 to 1.15, p=0.237). None of these differences reached statistical significance. A comparison of RR values based on sex, lesion length, age, and geographic region are presented in Figure 3B. The ABI after EVT remained similar in both groups, and there were no important shifts in the Rutherford category in either group.

Discussion

In this initial head-to-head study designed to assess the safety and efficacy of a NOAC (edoxaban) + aspirin as a dual antithrombotic treatment vs an antiplatelet (clopidogrel) + aspirin as DAPT after successful femoropopliteal EVT, the investigational regimen was at least as safe as the standard DAPT. Based on the TIMI classification, the more commonly used bleeding definition in the trials of guideline-recommended treatment (clopidogrel) vs other P2Y12 class antiplatelet agents,[20,22-25] there were no major or life-threatening bleeding events in the edoxaban group vs 4 (4%) in the clopidogrel group, although this difference was not statistically significant.

Using the ISTH bleeding definition, which is more commonly used in contemporary atrial fibrillation or venous thrombosis trials of OACs,[15,16,26,27] there was an excess of major bleeding events in the clopidogrel arm, but higher

Table 5. Efficacy for the mITT-2 Set.

Variable	Clopidogrel (n=101)[a]	Edoxaban (n=100)[a]	Relative Risk[b]
Restenosis/reocclusion[c]	33/95 (34.7) [25.3 to 45.2]	29/94 (30.9) [21.7 to 41.2]	0.89 [0.59 to 1.34]
Restenosis/reocclusion/TLR[c]	39/97 (40.2) [30.4 to 50.7]	32/95 (33.7) [24.3 to 44.1]	0.82 [0.53 to 1.18][d]
Restenosis/reocclusion/TLR/amputation[c]	40/97 (41.2) [31.3 to 51.7]	32/95 (33.7) [24.3 to 44.1]	0.82 [0.56 to 1.18]
Restenosis/reocclusion/TLR/amputation/MACE[c]	41/97 (42.3) [32.3 to 52.7]	32/95 (33.7) [24.3 to 44.1]	0.80 [0.55 to 1.15]
TLR	10/101 (9.9) [4.8 to 17.5]	11/100 (11.0) [5.6 to 18.8]	1.11 [0.49 to 2.50]
Amputation	4/101 (4.0)	1/100 (1.0)	
MACE	1/101 (1.0)	3/100 (3.0)	
Myocardial infarction	1/101 (1.0)	2/100 (2.0)	
Stoke	0	1/100 (1.0)	
Cardiovascular death	0	2/100 (2.0)	
All-cause mortality	0	3/100 (3.0)	

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; mITT, modified intention-to-treat set including all randomized subjects who received at least 1 dose of study drug and had at least 1 post-dose duplex ultrasound; TLR, target lesion revascularization.
[a]Data are presented as the count (percentage) [exact binomial 95% CI as appropriate].
[b]The 95% CI in brackets is calculated using a normal approximation to the binomial distribution unless specified otherwise.
[c]Based on patients who had duplex assessment.
[d]Relative risk and CI are calculated from logistic analysis with treatment, dose adjustment status at baseline, and stent placement as factors.

CRNM in the edoxaban arm; these were not statistically significant. Censoring vascular access bleeding events did not change the results.

There are no previously performed trials of dual antithrombotic agents with a NOAC in a similar peripheral EVT setting with which to compare the bleeding observations from this study. However, 2 trials in the PCI literature have used apixaban (APPRAISE-2) and rivaroxaban (ATLAS ACS 2-TIMI 51) as triple antithrombotic regimens; both are NOACs in the factor Xa inhibitor drug class.[28,29] In addition, the recently completed COMPASS trial compared rivaroxaban in combination with aspirin or given alone with aspirin monotherapy in patients in with stable atherosclerotic vascular disease.[30] The APPRAISE-2 trial was stopped due to unacceptable risk of bleeding in patients treated with apixaban plus DAPT compared with those treated with DAPT alone.[28] Using TIMI bleeding criteria, the ATLAS ACS 2-TIMI 51 trial reported a statistically significantly greater risk of major bleeding in the rivaroxaban plus DAPT arm (2.1%) compared with the DAPT arm (0.6%).[29] The COMPASS trial reported that ISTH-defined major bleeding events occurred more frequently in patients in the rivaroxaban + aspirin group vs the aspirin group (3.1% vs 1.9%, $p<0.001$).[30] Based on the observations with apixaban from APPRAISE-2 (the discontinued study) and the completed trials with rivaroxaban, which reported greater risk of bleeding complications, it is reasonable to conclude that the regimen of dual antithrombotic regimen (edoxaban + aspirin) has shown comparable bleeding risk with DAPT (clopidogrel + aspirin) and perhaps a signal for a lower bleeding risk, especially relative to major and life-threatening bleeding events by either TIMI or the more sensitive ISTH classifications. These results suggest that the concern over use of anticoagulants in the post-EVT setting because the risk of excess bleeding did not actualize in this study, which used an anticoagulant in a regimen with aspirin.

Duplex was used to evaluate restenosis/reocclusion (defined as PSVR ≥2.4[19]) at the treated segment to assess potential efficacy signals of edoxaban compared with conventional DAPT. All duplex evaluations were performed by readers who were blinded to treatment assignment. By 6 months, patients in the edoxaban treatment group had a lower relative risk of restenosis/reocclusion compared with the clopidogrel group. When the first occurrence of major amputation and major adverse cardiovascular events are considered along with restenosis/reocclusion or TLR, the relative risk reduction increased to 20% in favor of edoxaban, but these differences did not reach statistical significance. Of 5 major amputations in the study, 4 occurred in patients treated with clopidogrel vs one reported in the edoxaban group. The wide CIs seen in the measures of efficacy are a consequence of the small sample size. However, it is reassuring to note that all the point estimates suggest a likely better efficacy for a regimen with a NOAC.

It should be noted that the average lesion length observed in this study was, in general, slightly longer than those reported in the stent development studies for PAD. For instance, the average lesion length was about 7.5 cm in the THUNDER study (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries)[8] and 9.7 cm in the Vienna Absolute Trial.[31] In this study, the average lesion length was ~25% to 70% greater than observed in those studies. Nevertheless, the combined restenosis/reocclusion rate with clopidogrel reported here at 6 months (34.7%) is consistent with the rates reported in previous studies (eg, 43% in the THUNDER study and 33.5% in the Vienna Absolute Trial).[8,31]

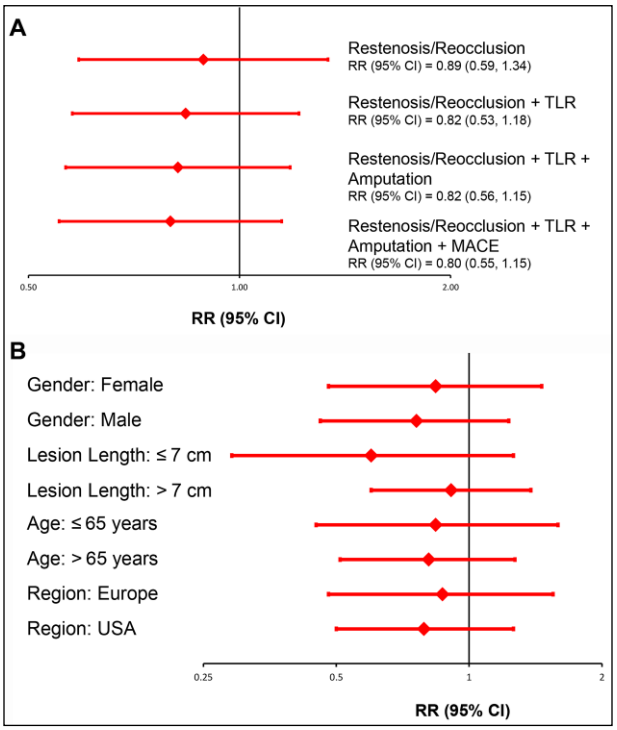

Figure 3. (A) Six-month event rates of the composite endpoints from the modified intent-to-treat analysis set, including all randomized subjects who received at least 1 dose of study drug and had at least 1 duplex ultrasound in follow-up. (B) A comparison of relative risks (RR) based on sex, lesion length, age, and geographic region. CI, confidence interval; MACE, major adverse cardiovascular events; TLR, target lesion revascularization.

Limitations

Our study has some methodological limitations that warrant discussion. Although p values are given, this study was not sized for formal statistical testing of safety or efficacy as this was a proof-of-concept study designed to reveal a signal for bleeding complications compared with conventional therapy. Therefore, an adequately sized trial will be needed to confirm the observations reported here.

Another limitation of the study is that it was open label, albeit randomized with central allocation and blinded endpoint adjudication; yet, the design may have accounted for greater propensity for patients and investigators to interrupt and/or discontinue the edoxaban treatment, which resulted in fewer cumulative patient years of exposure in that group. It is possible that this influenced the bleeding profile observed and minimized the efficacy signal being reported for edoxaban. In addition, thrombotic reocclusion and restenosis were not differentiated in this study.

Finally, the prevalence for higher-risk baseline characteristics is statistically similar; however, randomization is usually imperfect when the sample is small, as was the case in our study, and the study did not stratify patients based on bleeding risk. The consequence was numerical imbalances in some important covariates, such as more patients ≥75 years old, more women (greater risk of bleeding), fewer patients who used aspirin routinely, fewer patients who routinely used lipid-lowering treatment, more patients with a history of stroke, more patients with a history of atrial fibrillation, and more patients with renal disease in the edoxaban group. When viewed collectively, this suggests that the patients in the edoxaban group may have been at a greater risk of events.

Conclusion

The results from ePAD suggest that the combination of a NOAC (edoxaban) and aspirin may indeed be the optimal regimen for managing the major components of thrombosis and to minimize the risk of loss of patency following EVT in patients with PAD. An adequately sized randomized trial is needed to confirm these findings.

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