A randomized, open-label, parallel-group, multi-center study of adding edoxaban or clopidogrel to aspirin to maintain patency in subjects with peripheral arterial disease following femoropopliteal endovascular intervention-edoxaban in peripheral arterial disease (ePAD)

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The aim of this study is to evaluate whether adding edoxaban to aspirin following femoropoplitealendovascular intervention will enable maintenance of vessel patency and prevent restenosisrelative to current treatment with clopidogrel and aspirin.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON40071

Source
ToetsingOnline

Brief title
ePAD

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
narrowing of the peripheral arteries (mostly in the legs), periferal arterial disease

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Sankyo Development Ltd
Source(s) of monetary or material Support: Daiichi Sankyo

Intervention

Keyword: clopidogrel, edoxaban, ePAD, peripheral arterial disease

Outcome measures

Primary outcome

To evaluate clinically relevant bleeding (i.e., major or clinically relevant non-major bleeding) occurring during treatment or within 3 days of interrupting or stopping study drug.

- To evaluate re-stenosis/re-occlusion [defined as peak systolic velocity (PSV) ratio >/= 2.4] at the treated segments(s) measured at 1, 3 and 6 months after randomization using color coded duplex ultrasonography scanning (DUS).

Secondary outcome

- To evaluate any bleeding (major, clinically relevant non-major, and minor bleeding) occurring during treatment or within 3 days of interrupting or stopping study drug.

- To evaluate all other clinical and laboratory safety assessments including AEs, SAEs, and other events of special interest (i.e., hepatic events).

- To characterize the PK and PD of edoxaban in PAD subjects.

Other objectives

To evaluate:

- Change in the peak systolic velocity (PSV) ratio in the treated segment(s)

at 3 and 6 months compared to 1 month;

- Change from baseline ABI at 3 and 6 months; for ABI definition, see

Appendix 17.1.2.;

- Rutherford stage at 1, 3 and 6 months; for Rutherford stage classification,

see Appendix 17.1.1.;

- Symptomatic acute thrombosis;

- Target lesion revascularization (percutaneous or surgical);

- MACE (a composite of non-fatal myocardial infarction (MI)/non-fatal

stroke and death from cardiovascular causes);

- Fatal and non-fatal SEE;

- Amputations;

- All cause mortality.

Study description

Background summary

The current treatment post-infrainguinal intervention is DAPT [aspirin indefinitely and
clopidogrel for 1 to 3 months]. However, current practice is not supported by clinical
trial evidence.
As a consequence of endovascular intervention, platelets adhere to the subendothelium
that is exposed after dilatation of the artery. The subendothelial collagen activates
platelets and platelet aggregation is mediated via the fibrinogen receptor GP

IIb/IIIa. In addition, subendothelial tissue factor (TF) is exposed and forms a complex with Factor VIIa (FVIIa) that circulates in plasma, triggering the activation of coagulation factors and the formation of fibrin. Thus, inhibition of platelet aggregation as well as inhibition of coagulation and fibrin formation may be the optimal strategy to prevent thrombosis and subsequent re-stenosis/re-occlusion after endovascular intervention. Therefore this study proposes to use edoxaban 60 mg QD dosage for 3 months on a background of aspirin to assess whether this regimen is effective in maintaining vessel patency following femoropopliteal endovascular intervention compared to clopidogrel.

Study objective

The aim of this study is to evaluate whether adding edoxaban to aspirin following femoropopliteal endovascular intervention will enable maintenance of vessel patency and prevent restenosis relative to current treatment with clopidogrel and aspirin.

Study design

This study is a randomized, open-label, parallel-group, active-control, multi-center, proof-of-concept study in subjects with PAD, designed to assess the safety and potential efficacy of either edoxaban/aspirin or current treatment practice (dual antiplatelet therapy) with clopidogrel/aspirin following femoropopliteal endovascular intervention. Eligible subjects will include those with symptomatic PAD who have undergone successful intervention (with or without stent placement). Subjects will be stratified during randomization by clinical center/site, intervention with/without stent placement and by factors requiring edoxaban dosage adjustment. After confirmation that subjects meet all inclusion criteria and do not meet any exclusion criteria, and completion of written informed consent, subjects will be randomized and dosed as early as possible after adequate hemostasis (i.e., within 4 hours of hemostasis) through an interactive voice/web response system (IXRS) in a 1:1 ratio to either one of the two treatment arms:

1. Edoxaban 60 mg once daily (QD) on a background therapy of aspirin 100 mg QD regimen. (See Section 3.2.1.2 for instructions
on dose adjustments), or,
2. Clopidogrel 75 mg QD on a background therapy of aspirin 100 mg QD regimen.

The first dose of edoxaban 60 mg QD will be given as early as possible after adequate hemostasis (i.e., within
4 hours of hemostasis) and once daily thereafter for 3 months. A loading dose of clopidogrel 300 mg will be
given as the first dose (i.e., within 4 hours of hemostasis) followed by 75 mg QD thereafter for 3
months; The subjects will undergo color coded DUS at 1, 3 and 6 months. These ultrasound images will serve to
establish the primary efficacy endpoint (re-stenosis as defined by PSV ratio >= 2.4) in the treated segments(s)
measured at 1, 3 and 6 months.

Intervention

1. Edoxaban 60 mg once daily (QD) on a background therapy of aspirin 100 mg QD regimen. (See Section 3.2.1.2 for instructions
on dose adjustments), or,
2. Clopidogrel 75 mg QD on a background therapy of aspirin 100 mg QD regimen.

Study burden and risks

The study takes 180 days (6 months) and the patient will be invited to the clinic 7 times for the purposes of this study. The visits will last approximately 2 hours. During these visits, the patient will undergo duplex Ultrasound scans, a physical exam, vital signs will be checked, questions will be asked, blood and urine will be collected and an electrocardiogram will be taken.

Edoxaban has a rapid and predictable onset of anticoagulant action. It has the potential to
be as efficacious as LMWH and vitamin K antagonists because it directly inhibits FXa.
Additional advantages of edoxaban are that it is an oral agent and thus more convenient
to use than anticoagulants that require intravenous (IV) or subcutaneous (SC) injections.
Second, unlike vitamin K antagonists (VKA), edoxaban does not require regular laboratory monitoring to control its anticoagulant effect and to minimize the risk of
serious bleeding.

The aim of this study is to evaluate whether adding edoxaban to aspirin following femoropopliteal
endovascular intervention will enable maintenance of vessel patency and prevent restenosis
relative to current treatment with clopidogrel and aspirin.

The most common side effects seen with edoxaban are bleeding and changes in liver blood tests. The most common side-effect of clopidogrel is bleeding, and uncommonly can result in bleeding inside the head or brain (a rare condition that causes a stroke or death). Aspirin (acetylsalicylic acid) may have undesirable side effects. People who are allergic to acetylsalicylic acid, or have asthma, persisting or recurring stomach problems (such as heartburn, upset stomach, or stomach pain), ulcers, or bleeding problems should not take aspirin, unless directed by a doctor.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

1. Male or female subjects older than the minimum legal adult age (country specific);
2. Rutherford stages 2-5; provided there are no ulcerations on the heel and/or exposed tendon and/or bone
3. Superficial femoral above knee-popliteal (3 cm proximal to the medial femoral condyle) lesion and >= 50% stenosis or occlusion;
4. At least one run-off vessel to the foot with or without additional endovascular intervention
5. Successful intervention, defined as angiographic confirmation of <= 30% residual stenosis and absence of flow limiting dissection;
6. Adequate hemostasis at the vascular access site within 24 hours of intervention;
7. A subject is also eligible if they have undergone additional successful endovascular intervention(s) during the index intervention;
8. Able to provide signed informed consent.

Exclusion criteria

1. Calculated creatinine clearance (CrCL) <30 ml/min;
2. Femoral or popliteal aneurysm;
3. Adjunctive use of thrombolytics;
4. Any extravasation or distal embolization not successfully treated;
5. Uncontrolled hypertension as judged by the investigator (e.g., systolic blood pressure >170 mmHg or diastolic blood pressure >100 mmHg despite antihypertensives)
6. Aspirin intolerance;
7. Clopidogrel intolerance;
8. Contraindication for anticoagulants or antiplatelets and any other contraindication listed in the local labeling of aspirin and/or clopidogrel (see Appendix 17.8 for US and EU labeling);
9. Active bleeding or known high risk for bleeding or history of intracranial, or spontaneous intraocular, spinal retroperitoneal or intra-articular bleeding; overt gastrointestinal (GI) bleeding or
active ulcer within the previous year;
10. Subjects receiving dual antiplatelet or anticoagulant therapy at the time of randomization; subjects receiving preinterventional loading dose of clopidogrel or other P2Y12 receptor antagonists;
11. Treatment with cilostazol within 24h of randomization
12. Subjects receiving prohibited concomitant medications [fibrinolytics, chronic use of non steroidal anti-inflammatory drugs (NSAIDS) > 4 days per week, and oral or parenteral non-aspirin NSAIDs and strong P-gp inhibitors];
13. Prior stroke or MI or acute coronary syndrome within 3 months;
14. Chronic liver disease [alanine transaminase (ALT) and/or aspartate transaminase (AST) >=
2 × upper limit of normal (ULN); total bilirubin (TBL) >= 1.5 ×ULN]; however, subjects whose elevated TBL is due to known Gilbert*s syndrome may be included in the study;

15. Prior history of a positive test for Hepatitis B antigen or Hepatitis C antibody;
16. Subjects who received any investigational drug or device within 30 days prior to randomization, or plan to receive such investigational therapy during the study period;
17. Subjects previously randomized to an edoxaban (DU-176b) study;
18. Women of childbearing potential without proper contraceptive measures (i.e. a method of contraception with a failure rate < 1 % during the course of the study including the observational period) and women who are pregnant or breast feeding;
Note: These methods of contraception according to the note for guidance on nonclinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence, and vasectomy for the male partner;
19. Subjects with the following diagnoses or situations:
- Active malignancy except for adequately treated non-melanoma skin cancer or other non-invasive or in-situ neoplasm (e.g., cervical cancer in situ);
- Concurrent treatment with cancer therapy (drugs, radiation, and/or surgery);
- Other significant active concurrent medical illness or infection;
- Life expectancy < 12 months;
20. Subjects who are unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for subsequent visits,and/or otherwise considered by the Investigator to be unlikely to complete the study);
21. Subjects with any condition that, in the opinion of the Investigator, would place thesubject at increased risk of harm if he/she participated in the study;
22. History of heparin-induced thrombocytopenia.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	11-07-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	aspirine
Generic name:	acetylsalicylic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Edoxaban Tosylate
Generic name:	DU-176b
Product type:	Medicine
Brand name:	Plavix
Generic name:	clopidogrel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-01-2013
Application type:	First submission
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	27-03-2013
Application type:	First submission
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	03-05-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO	

Date:	16-05-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

Approved WMO Date:	25-11-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

Approved WMO Date:	28-11-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

Approved WMO Date:	16-04-2014
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-003009-88-NL
CCMO	NL42559.101.12

Study results

Date completed: 02-12-2014

Actual enrolment: 14

Summary results
Trial is onging in other countries