Evaluation of the safety and efficacy of an edoxaban-based compared to a vitamin K antagonist- based antithrombotic regimen following successful percutaneous coronary intervention (PCI) with stent placement (ENTRUST_AF PCI)

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The primary objective is to compare a 12-month antithrombotic regimen of edoxaban in combination with clopidogrel or another P2Y12 antagonist against a regimen of a vitamin K antagonist (VKA) in combination with clopidogrel or another P2Y12...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON46857

Source
ToetsingOnline

Brief title
ENTRUST-AF PCI

Condition

- Cardiac arrhythmias
- Embolism and thrombosis

Synonym

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Thrombosis after a percutaneous coronary intervention with stent placement, Thrombosis after angioplasty with stent placement

Research involving
Human

Sponsors and support

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

Intervention

Keyword: antithrombotic regimen, Edoxaban, PCI, stent placement

Outcome measures

Primary outcome

The primary endpoint is the composite of major or clinically relevant non-major bleeding (MCRB) defined according to the ISTH bleeding definitions, analyzed as time to first occurrence of any component.

Secondary outcome

- Main efficacy endpoint (MEE), defined as the composite of cardiovascular (CV) death, stroke, systemic embolic events (SEE), spontaneous myocardial infarction (MI) and definite stent thrombosis (as per ARC consensus definitions).

- Net clinical benefit (NCB), defined as the composite of CV death, stroke, SEE, spontaneous MI, definite stent thrombosis and ISTH-defined major bleeding.

- Main thromboembolic event, defined as composite of cardiac or thromboembolic death (thromboembolic death considered to be thromboembolic in origin (including thromboembolic stroke, pulmonary embolism, any other systemic embolism), ischemic stroke, SEE, spontaneous MI and definite stent thrombosis.

- ISTH-defined major bleeding

- Any bleeding defined as the composite of major, clinically relevant non-major and minor bleeding (ISTH definition)

- Symptomatic intracranial hemorrhage (ICH)

- Composite of stroke and SEE

- Composite of all-cause death, stroke, SEE, spontaneous MI and definite stent thrombosis

- Composite of CV death, spontaneous MI and definite stent thrombosis

- The single components of the composite primary and secondary endpoints mentioned above are explored, as well as specific subcategories (e.g., hemorrhagic, ischemic and undetermined stroke)

Study description

Background summary

The optimal antithrombotic (*blood thinning*) therapy in patients with atrial fibrillation (AF) following stenting of an artery close to the heart (coronary artery) is unknown at this time and is the subject of this investigation.

There are two main types of blood thinners. Anticoagulants, such as edoxaban or vitamin-K antagonists (VKA), lengthen the time it takes to form a blood clot. Antiplatelet drugs, such as aspirin and so called P2Y12 inhibitors, prevent blood cells called platelets from clumping together to form a clot. Anticoagulants are typically used in patients with atrial fibrillation, a combination of aspirin and a P2Y12 inhibitor in patients following coronary artery stenting.

Edoxaban has been developed as an alternative to VKA and has already been allowed for clinical use in European countries for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, high blood pressure, age * 75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA).

In this study, edoxaban will now be given to patients who have atrial

fibrillation AND have undergone a successful coronary artery stenting. Edoxaban in combination with P2Y12 will be compared to a VKA in combination with aspirin and a P2Y12 inhibitor for safety towards bleeding and efficacy towards thrombotic complications like stroke.

Study objective

The primary objective is to compare a 12-month antithrombotic regimen of edoxaban in combination with clopidogrel or another P2Y12 antagonist against a regimen of a vitamin K antagonist (VKA) in combination with clopidogrel or another P2Y12 antagonist and 1-12 months ASA in subjects with AF following successful PCI with stent placement in terms of the incidence of major or clinically relevant non-major ISTH-defined bleeding (MCRB).

There are two primary hypotheses for bleeding to be tested consecutively in this study.
· The edoxaban-based antithrombotic regimen is non-inferior to the VKA-based antithrombotic regimen with regards to MCRB.
· The edoxaban-based antithrombotic regimen is superior to the VKA-based antithrombotic regimen with regards to MCRB.

These two hypotheses are tested in a hierarchical manner, non-inferiority followed by superiority to control the type-I error rate, with adequate power for each of the two hypotheses.

Secondary exploratory objectives of the study are to compare the edoxaban-based antithrombotic regimen to the VKA-based antithrombotic regimen with regard to:
· Main efficacy endpoint (MEE), defined as the composite of cardiovascular (CV) death, stroke, systemic embolic events (SEE), spontaneous myocardial infarction (MI) and definite stent thrombosis.
· Net clinical benefit (NCB), defined as the composite of CV death, stroke, SEE, spontaneous MI, definite stent thrombosis and ISTH-defined major bleeding.
· Main thromboembolic event, defined as composite of cardiac or thromboembolic death, ischemic stroke, SEE, spontaneous MI and definite stent thrombosis.
· ISTH-defined major bleeding
· Any bleeding defined as the composite of major, clinically relevant non-major and minor bleeding (ISTH definition)
· Symptomatic intracranial hemorrhage (ICH)
· Composite of stroke and SEE
· Composite of all-cause death, stroke, SEE, spontaneous MI and definite stent thrombosis
· Composite of CV death, spontaneous MI and definite stent thrombosis
· The single components of the composite primary and secondary endpoints mentioned above are explored.
· Safety parameters such as (serious) adverse events, laboratory parameters, ECG and vital signs.

Study design

This is a multinational, multicenter, randomized, open-label Phase 3b study with blinded evaluation of endpoints by an independent Clinical Event Committee (CEC) [PROBE design]. An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring safety during the study.

Subjects eligible to participate in the study provide written informed consent (IC) before randomization or any study-specific procedures. Once written IC is obtained, subject should be randomized without delay via an interactive voice and web response system (IXRS).

The Investigator should be prepared to provide subject information, including, but not limited to: age, body weight, clinical presentation (ACS or stable coronary disease), CrCL using Cockcroft-Gault formula (see Section 17.6) and whether the subject is taking certain concomitant P-gp inhibitors (see Section 5.3.1).
Randomization is stratified by clinical presentation (ACS or stable coronary disease), requirement for dose adjustment of edoxaban (60 or 30 mg), and geographical region. Subjects are assigned randomly via the above mentioned IXRS such that the study has a 1:1 ratio of subjects in the two antithrombotic treatment regimens:

*Edoxaban-based regimen for 12 months:
1. Edoxaban 60 mg once-daily or 30 mg once-daily in selected subjects (see below *Dosage Form, Dose, and Route of Administration* and Section 5.3.1).

2. Clopidogrel 75mg once-daily (or in the presence of a documented clinical need prasugrel [5mg or 10 mg once-daily] / ticagrelor [90 mg twice-daily] may be used).

3. Concomitant use of another anti-platelet agent (i.e. ASA) is not allowed.

*VKA-based regimen for 12 months:
1. The VKA of choice with once-daily dosing for target international normalized ratio (INR) between 2.0 to 3.0, inclusive.

2. Clopidogrel 75mg once-daily (or in the presence of a documented clinical need prasugrel [5mg or 10 mg once-daily] / ticagrelor [90 mg twice-daily] may be used).

3. ASA (100 mg once-daily) for a minimum of 1 month and up to 12 months duration at the Investigator discretion guided by the clinical presentation (ACS or stable coronary disease), and upon the CHA2DS2-VASc and HAS-BLED score.
(1)

4. The use of a P2Y12 antagonist other than clopidogrel must be pre-declared, together with the intended duration of ASA treatment.

All dosage adjustments are implemented through the IXRS. The IXRS provides the appropriate drug supply kit number based on
the subject*s information as provided by the Investigator.

Note: For simplicity, this protocol uses the term *edoxaban* to refer to edoxaban tosylate, *clopidogrel* to refer to clopidogrel bisulfate and the term * prasugrel* to refer to prasugrel hydrochloride.

Intervention

Edoxaban: 60, 30 and 15 mg provided as film coated tablets for oral use.
Subjects receive 60 mg edoxaban once-daily. A dose reduction (30 mg edoxaban once-daily) is determined for subjects with one
or more of the following factors:
-*Moderate or severe renal impairment (CrCL 15 * 50 mL/min)
-*Low body weight * 60 kg (132 lbs),
-*Concurrent use of P-gp inhibitors (please refer to local summary of product characteristics [SmPC] or to the Investigator Brochure [IB], as applicable);

In EU countries, according to SmPC concomitant use of edoxaban with cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once-daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction.

For low body weight (* 60 kg) present at randomization, the edoxaban dose is reduced permanently and even if the subject gains weight, the edoxaban dose remains reduced. The dose of edoxaban returns to the regular dosage regimen of 60 mg once daily any time the subject no longer displays any of the other above mentioned factors.

After randomization and in subjects without dose reduction, if subject*s:
- body weight drops to * 60 kg and the body weight change is > 10% of the subject*s baseline body weight, then the edoxaban dose is reduced (i.e. to 30 mg once-daily) permanently.

- CrCL becomes 15 to 50 mL/min and the CrCL change is >20% of the subject*s baseline CrCL, then the edoxaban dose is reduced.

- Develops the need for concomitant treatment with P-gp inhibitors (except quinidine, verapamil or amiodarone), then the edoxaban dose is reduced (i.e. to 30 mg once daily).

The dose of 15 mg edoxaban once-daily is not indicated as monotherapy and is solely provided as part of transition from edoxaban 30 mg at the end of study

(see Section 5.3.3).

VKA: Oral VKA of choice, as pre-defined per country, with once daily dosing for target INR between 2.0 to 3.0, inclusive.

VKA is supplied as commercially available tablets of the preferred VKA for each selected country participating in the study, being either:
*Warfarin: 1 and 2.5 mg tablets.
*Phenprocoumon: 3 mg tablets.
*Fluindione: 20 mg tablets (exclusive to France).
*Acenocoumarol: 4 mg en 1mg tablets.

The Investigator monitors the INR and adjusts the VKA dose to maintain the INR within target. It is the Investigators responsibility to collect monthly INR assessments and record these throughout the study.

P2Y12 antagonist:
*Clopidogrel 75 mg, oral commercially available tablets.

Subjects receive clopidogrel 75 mg once-daily according to the prescribing information, or in the presence of a documented clinical need (e.g. but not restricted to known clopidogrel nonresponder), either

o Prasugrel 5 or 10 mg, oral commercially available tablets.

Subjects receive prasugrel 10 mg once-daily or prasugrel 5 mg once-daily if * 75 years of age or * 60 kg (132 lb), according to the prescribing information.

o Ticagrelor 90 mg, oral commercially available tablets.

Subjects receive ticagrelor 90 mg twice-daily according to the prescribing information.

Acetylsalicylic acid (ASA): 100 mg, oral commercially available tablets.

Subjects assigned to the VKA-based regimen receive 100 mg once-daily of ASA. In subjects assigned to the edoxaban-based regimen ASA is not allowed.

Sponsor supplies participating sites with study medication, consisting of edoxaban, VKA (country pre-defined), P2Y12 antagonist (clopidogrel, prasugrel or ticagrelor), and ASA. Please refer to the local SmPC or IB for edoxaban as applicable and to the SmPC of each other study medication.

All dosage adjustments are implemented through the IXRS. The IXRS provides the appropriate drug supply kit number based on the subject*s information as provided by the Investigator.

Study burden and risks

There are risks and discomforts and inconveniences associated with any research study. For this study an independent Data and Safety Monitoring Board (DSMB) will assess the overall study status and safety of subjects at intervals outlined in the DSMB charter and will make recommendations to the Executive Committee on continuing or modifying the study based on these assessments.

Patients will be required to visit the hospital and undergo tests and procedures more frequently than standard practice, however, these visits and procedures are required to ensure patient safety by close monitoring of the patient*s health.

Side Effects:
Participants may experience side effects from the drugs used in this study. The most common risks or side effects are the same for the study drug edoxaban and the other drug VKA which is already prescribed as standard care. They are seen in 1-9% of the patients taking edoxaban or a VKA. These risks and side effects may be minor (no doctor visit is necessary) or major (help from doctor/hospital is necessary. The most common side effect is bleeding. More detailed on the potential side effects can be found in the pis icf. Chiltern have robust Pharmo Vigilance procedures in place. In addition the sponsor have an independent Data and Safety Monitoring Board (DSMB) in place to protect the rights, safety and well-being of participants in this study.

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.OAC indication for atrial fibrillation for a period of at least 12 months following successful PCI with stenting in adult male and female patients *18 years of age. Eligibility is assessed 4 hours after sheath removal and within 5 days after successful PCI with stent placement. If a staged PCI is planned, eligibility is assessed after completion of the last stage.;Successful PCI definition:
The success of a PCI procedure is defined by 2 interrelated components:
angiographic findings, procedural / clinical outcomes as detailed below:
- Angiographic Success
- A minimum stenosis diameter of < 20% (as visually assessed by angiography - residual blockage or stenosis reduced to less than 20% of the artery's diameter).
- Sufficient enlargement of the lumen at the target site to improve coronary artery blood flow with final TIMI flow grade 3 (visually assessed by angiography), without occlusion of a significant side branch, flow-limiting dissection, distal embolization, or angiographic thrombus.;Procedural Success:
No major in-hospital clinical complications(e.g. ongoing ISTH, major or clinical relevant non-major procedural bleeding at the time of randomization, stroke, emergency CABG).;In summary, a clinically successful PCI requires both anatomic and
procedural success along with relief of signs and/or symptoms of myocardial ischemia at the time of randomization.

Exclusion criteria

Bleeding risks or systemic conditions
1.Known bleeding diathesis, including but not limited to,
a.Uncontrolled active bleeding, encompassing both ISTH major and clinically relevant non-major bleeding, preceding randomization.
b.Lesion or condition, if considered to be a significant risk for major bleeding.
This may include but is not limited to: unresolved gastrointestinal

ulceration, presence of malignant neoplasms at high risk of bleeding (e.g. malignancies with metastasis), recent unresolved brain or spinal injury, recent brain, spinal or ophthalmic surgery, any intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms (of more than 3.5 cm) or major intraspinal or intracerebral vascular abnormalities.;Medication-related
2.INR > 2.5 (the subject can be reconsidered at a later time, but within 5 days of sheath removal).
3.Contraindication to edoxaban, VKA, ASA and/or P2Y12 antagonists;
4.Concomitant treatment with other antithrombotic agents, fibrinolytic therapy and chronic nonsteroidal anti-inflammatory drugs (NSAIDs).;Concomitant conditions and therapies
5. Critically ill or hemodynamically unstable subjects (at the time of randomization) including:
a.cardiogenic shock or acute decompensated heart failure, with the requirement for vasopressor agents or inotropic support or mechanical support to support circulation
b.respiratory failure requiring endotracheal intubation and mechanical ventilation.
6.Any prior mechanical valvular prosthesis;
7.Planned coronary or vascular intervention or major surgery within 12 months; Randomization must be deferred to the last stage in a multistep, multivessel PCI procedure;
8.Moderate or severe mitral stenosis;
9.Ischemic stroke within 2 weeks prior to randomization;
10.Uncontrolled severe hypertension with a systolic blood pressure (BP) *180 mmHg and/or diastolic BP * 120 mmHg;
11.Severe renal impairment with estimated creatinine clearance (CrCL) < 15 mL/min or on dialysis;
12.Known abnormal liver function prior to randomization (incl. hepatic disease or biochemical evidence of significant liver derangement known prior to randomization;Other exclusion criteria
13.Any of the following abnormal local laboratory results prior to randomization:
a.Platelet count < 50 x109/L
b.Hemoglobin < 8 mg/dL
14.Unable to provide written IC;
15.Female subjects of childbearing potential without using highly effective contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilised, or has not had a hysterectomy at least three months prior to the start of this study). Females taking oral contraceptives should have been on therapy for at least three months. Adequate contraceptives include: Combined (estrogen and progestogen
containing) oral, intravaginal, transdermal, hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence);
16.Pregnant or breast-feeding subjects;

17.Assessment that the subject is not likely to comply with the study procedures or have complete follow-up;
18.Participating in another clinical trial that potentially interferes with the current study;
19.Previous randomization in this study;
20.Active on prescription drug abuse and addiction; abuse of illicit substances (i.e. marijuana, cocaine, methamphetamine, heroin) and alcohol abuses during the last 12 months according to the judgement of the investigator;
21.Life expectancy < 12 months.

Study design

Design

Study phase:	3
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):	21-11-2017
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	acenocumarol
Generic name:	acenocumarol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	acetylsalicylic acid

Generic name:	acetylsalicylic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	clopidogrel
Generic name:	clopidogrel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lixiana
Generic name:	edoxaban
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	phenprocoumon
Generic name:	phenprocoumon
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-10-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-02-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-05-2017
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2016-002683-14-NL
ClinicalTrials.gov	NCT02866175
CCMO	NL58918.100.16