Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation * In Atrial Fibrillation.

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* To assess the effect of Edoxaban versus vitamin K antagonist (VKA) on net adverse clinical events (NACE), i.e., the composite of all-cause death, myocardial infarction (MI), ischemic stroke, systemic thromboembolism (SEE), valve thrombosis, and...

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

Summary

ID

NL-OMON50179

Source
ToetsingOnline

Brief title
ENVISAGE-TAVI AF

Condition

- Cardiac arrhythmias

Synonym
arrythmia in patients that had a transplantation of a aortic valve

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Atrial Fibrillation, Edoxaban, Transcatheter Aortic Valve Implantation

Outcome measures

Primary outcome

Efficacy endpoints:

* NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major and minor bleeding per TIMI definitions

* NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (Bleeding Academic Research Consortium [BARC] 3 or 5 definition)

* NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major and moderate bleeding (Global Utilization of Streptokinase And Tissue Plasminogen Activator For Occluded Coronary arteries [GUSTO] definition)

* Major Adverse Cardiac Events (MACE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, or repeat coronary revascularization of the target lesion

* Major Adverse Cardiac and Cerebrovascular Events (MACCE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, stroke (ischemic, hemorrhagic, or undetermined), or repeat coronary revascularization of the target lesion

* Cardiovascular mortality

* Stroke (ischemic, hemorrhagic, or undetermined)

* Stroke (ischemic)

* Stroke (hemorrhagic)

* Stroke (undetermined)

* Fatal stroke (ischemic, hemorrhagic, or undetermined)

* Non-fatal stroke (ischemic, hemorrhagic, or undetermined)

* SEE

* Myocardial Infarction

* Valve thrombosis

Safety endpoints:

* Bleeding defined as TIMI major and minor, BARC 3 or 5, and GUSTO moderate or severe

* Bleeding defined as ISTH major and CTNM, TIMI major/minor bleeds or requiring medical attention, BARC 2, 3 or 5, and GUSTO moderate or severe

* Bleeding defined as ISTH, CRNM, TIMI minor or requiring medical attention, BARC 2, and GUSTO moderate

* All bleeding that are not ISTH major, CRNM, TIMI minimal, BARC 1 non-actionable, and GUSTO mild

* Any bleeding

* Intracranial hemorrhage

* Life-threatening bleeding

* Fatal bleeding (fulfilling the ISTH major bleeding definition)

* Non-fatal major bleeding (ISTH definition)

* All-cause mortality

* Cardiovascular mortality

* Safety parameters such as (serious) adverse events, laboratory parameters, ECG and vital signs

Secondary outcome

* Number of hospital admissions, defined as * 24 h stay in the hospital, due to cardiovascular causes (post TAVI and non-TAVI procedure related), including but not limited to overall, for bleeding, SEE, venous thrombosis, shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.)
o Note: Hospital admissions due to cardiovascular causes include, but are not limited to Emergency Department (ED), Intensive Care Unit (ICU), cardiovascular ward
* Treatment satisfaction as assessed by the Perception Anticoagulant Treatment Questionnaire (PACT-Q)
* Health related quality of life as assessed by the EuroQoL (EQ-5D-5L) Questionnaire
* Biomarker of hemostasis such as but not limited to markers of coagulation and aggregation (sub-study) such as whole blood clotting time (WBCT), thrombelasto-graphy (TEG), multiple electrode aggregometry (MEA)

Study description

Background summary

Degenerative aortic valve stenosis is the second most common valvular disorder in
Europe and in the United States. Transcatheter aortic valve implantation (TAVI) is a life-saving
procedure for patients with severe aortic stenosis and high risk for surgery. Bleeding complications and cerebrovascular events following TAVI are a matter of concern. Patients undergoing TAVI are elder, frail, and at high risk for both stroke and bleeding. This risk increases exponentially in patients with atrial fibrillation or other indications to chronic anticoagulation therapy. Balancing the risk of both bleeding and thrombotic events in this population is challenging. Moreover, optimal anti-thrombotic therapy after TAVI is still unknown. Therefore the use of a direct factor Xa inhibitor such as Edoxaban in patients undergoing TAVI may be an attractive option in order to prevent thromboembolic and bleeding events.

Study objective

* To assess the effect of Edoxaban versus vitamin K antagonist (VKA) on net adverse clinical events (NACE), i.e., the composite of all-cause death, myocardial infarction (MI), ischemic stroke, systemic thromboembolism (SEE), valve thrombosis, and major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition).
* To assess the effect of Edoxaban versus VKA on major bleeding (ISTH definition).

Study design

This is a multinational, multicenter, prospective, randomized, open-label study with blinded evaluation of endpoints (PROBE) parallel group study comparing Edoxaban with VKA in subjects with AF having undergone TAVI. Critical events will be adjudicated by an independent Clinical Event Committee (CEC). An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring safety during the study.

Intervention

* Edoxaban-based regimen:
Edoxaban 60 mg once-daily or 30 mg once-daily in selected subjects (dose reduction criteria according to locally approved label).

* VKA-based regimen:
The VKA of choice (any locally approved), dose-adjusted throughout the study for target international normalized ratio (INR) between 2.0 to 3.0 (numbers inclusive).

Study burden and risks

The main risk of treatment with Edoxaban is bleeding. This is similar to the risk of standard of care treatment with VKA. Therefore, the main "risks" of participation in the study are more the additional burden study participation entails (blood draws, time input, etc.).
Overall, edoxaban has an adequately characterized positive benefit-risk ratio in large and representative populations globally in patients with NVAF and VTE, demonstrating efficacy in the overall populations and subgroups in conjunction with a favorable bleed profile as well as demonstrating its effectiveness in a dose-dependent manner for VTE prevention after orthopedic surgery such as hip or knee
replacement. Additional advantages of edoxaban are its QD dosing, dose reduction strategies to minimize the risk of bleeding with preserved efficacy and no necessity for constant monitoring of therapy.

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

Subjects must satisfy all of the following criteria to be included in the study:, 1. Successful TAVI via transvascular access route such as to the femoral, carotid, axillary, and subclavian arteries. Other access routes need prior approval per majority vote from 3 members of the Executive Committee (both Global Lead Investigators and the Daiichi Sankyo Medical Lead or his/her designee); success is defined as:, a. Correct positioning of a single prosthetic heart valve into the proper anatomical location
b. Presence of all 3 conditions post TAVI
i. Mean aortic valve gradient <20 mm Hg
ii. Peak transvalvular velocity <3.0 m/s
iii. Aortic valve regurgitation of 2 or less
c. No clinically overt stroke
d. No uncontrolled bleeding at time of randomization, 2. Indication for chronic OAC
a. Documented pre-existing AF
b. New onset AF (e.g. >30 seconds documented by ECG), 3. Provision of signed informed consent, 4. Age *18 years

Exclusion criteria

1. Conditions with a high risk of bleeding
This may include but is not limited to: active peptic ulcer with upper gastrointestinal bleeding within last 90 days prior to randomization, malignancy at high risk of bleeding, major intraspinal or intracerebral vascular abnormalities, recent unresolved brain or spinal injury, or spinal surgery (recent = within the last 90 days prior to randomization), any intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, or clinically relevant vascular aneurysms., 2. Other known bleeding diatheses, 3. Conditions that make it difficult for the subject to swallow the study medication , 4. Serious unresolved periprocedural complications, 5. Any contraindications to EITHER Edoxaban OR VKA, per local label; this includes hypersensitivity to the active ingredient, to any of the excipients, or any of the components of the study medications, 6. Concomitant treatment with other antithrombotic agents, ASA >100 mg/day, fibrinolytic therapy, or chronic (> 4 days/week) use of nonsteroidal antiinflammatory drugs (NSAIDs); however, NSAID patches are permitted, 7. Requirement for dual-antiplatelet therapy (DAPT) at randomization that will be indicated for more than 3 months beyond the first OAC dose., 8. Treatment with other investigational drugs (i.e. non-approved) or devices within 30 days before enrollment or planned use of investigational drugs or devices during the study, For full list of Exclusion criteria: Refer to Protocol, section: 4.2

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):	06-10-2017
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Acenocoumarol
Generic name:	Acenocoumarol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Edoxaban
Generic name:	Edoxaban
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Phenprocoumon
Generic name:	Phenprocoumon
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-05-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	01-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (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	EUCTR2016-003930-26-NL
ClinicalTrials.gov	NCT02943785
CCMO	NL60356.078.17