Effect of Bivalirudin on Aortic Valve Intervention Outcomes 2/3

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The objective of the BRAVO 2/3 study is to assess the safety and efficacy of using bivalirudin instead of unfractionated heparin (UFH) in transcatheter aortic valve replacements (TAVR).

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

Summary

ID

NL-OMON39580

Source
ToetsingOnline

Brief title
BRAVO 2/3

Condition

- Cardiac valve disorders

Synonym
severe aortic stenosis, severe narrowing of a aorta valve

Research involving
Human

Sponsors and support

Primary sponsor: Medicines Company
Source(s) of monetary or material Support: The Medicines Company

Intervention

Keyword: Aortic Valve Intervention, Bivalirudin, Bleeding, TAVR

Outcome measures

Primary outcome

The primary end point will be major bleeding defined as Bleeding Academic Research Consortium (BARC) type >=3b at 48 hours or hospital discharge whichever occurs first. BARC type 3b bleeding includes bleeds that are evident clinically, or by laboratory or imaging results, which result in surgical intervention or administration of intravenous vasoactive drugs; overt bleeds with a hemoglobin drop of at least 5g/dL; and bleeding that causes cardiac tamponade. BARC 3c bleeding includes intracranial or intraocular bleeds that compromise vision. BARC type 4,CABG related bleeding, includes perioperative intracranial bleeding within 48 hours; bleeds that result in reoperation following closure of sternotomy for the purpose of controlling bleeding; bleeds that result in treatment with transfusion of >=5 units of whole blood or packed red blood cells within a 48 hour period; and chest tube output >= 2L within a 24 hour period. BARC type 5, fatal bleeding, describes bleeds that directly result in death with no other cause. The co-primary endpoint will be net adverse cardiac events (NACE) at 30 days that is the composite of major adverse cardiovascular events (MACE) + major bleeding (BARC type >=3b). The composite of major adverse cardiovascular events (MACE) is defined as all-cause mortality, myocardial infarction, and stroke. All events will be adjudicated using source documents by an independent clinical events committee blinded to the antithrombotic agents.

Each component of the co-primary endpoint will be tested in a hierarchical manner with a superiority test for bleeding followed by a non-inferiority and then superiority test for NACE.

Secondary outcome

The secondary endpoints of this trial are:

(1) Major bleeding according to additional scales (VARC, TIMI, GUSTOACUITY/HORIZONS);

(2) Bleeding BARC >=3; moderate bleeding BARC = 3a;minor bleeding (BARC type 1 and 2 and TIMI minor)

(3) major adverse cardiac events (MACE) including death, non-fatal MI, and stroke;

(4) the rates of the individual components of MACE;

(5) transient ischemic attack;

(6) acute kidney injury;

(7) VARC major vascular complications;

(8) acquired thrombocytopenia;

(9) rate of new post-procedural atrial fibrillation/flutter;

(10)economic analysis of using bivalirudin in TAVR.

All end points will be assessed at 48 hours post-procedure (or prior to hospital discharge, if that occurs earlier) and up to 30-days. With respect to the economic analysis, the analysis time point will be fixed to the hospital discharge (but also include any subsequent hospitalizations).

Study description

Background summary

The BRAVO 2/3 study is an international, multicenter, open-label, randomized controlled trial. The objective of the BRAVO 2/3 study is to assess the safety and efficacy of using bivalirudin instead of unfractionated heparin (UFH) in transcatheter aortic valve replacements (TAVR). The hypothesis is that bivalirudin will reduce bleeding rates compared to UFH, and will improve the overall clinical outcomes of TAVR patients.

Study objective

The objective of the BRAVO 2/3 study is to assess the safety and efficacy of using bivalirudin instead of unfractionated heparin (UFH) in transcatheter aortic valve replacements (TAVR).

Study design

This is an international, multicenter, open-label, randomized controlled, phase III trial. All patients undergoing transfemoral TAVR at the participating centers will be eligible. All sites will initiate enrolment with 2 feasibility roll-in bivalirudin treated patients and thereafter patients will be randomly assigned to either standard dosing of bivalirudin or UFH as control. The 2 roll-in cases per site will constitute the feasibility cohort that will be followed and analyzed separately. Patients will undergo TAVR according to current standard of care practices at the treating centers. Use of antiplatelet agents pre, during, and post procedure, and possibly oral anticoagulants post procedure, will be according to the sites* standard practice. ALL available data will be collected in the eCRF prospectively.

Intervention

No additional interventions or procedures are planned or required other than the standard procedures (or physician standard practice) of the hospital for patients that undergo a TAVR procedure.

During the planned TAVR procedure, the subject will receive either UFH as standard care or bivalirudin by intravenous infusion until successful valve treatment.

Study burden and risks

Most procedures are performed as per standard physician*s practice for subjects selected for TAVR.

Study specific procedures for the subject (this is additional to all standard physician*s practice (ECGs, ECHOs and other (blood) sampling or procedures)):
-ICF procedure
-Serum Creatinine values need to be measured according to the protocol for four times.

Risks for the patient:
-Haemorrhage at any site (minor haemorrhage is very common((>=1/10), major heamorrhage is common (>=1/100 to <1/10). This includes access site haemorrhage (common, affects fewer than 1 in 10 patients), gastrointestinal haemorrhage, epistaxis or haematuria (uncommon, affects fewer than 1 in 100 patients). Bleeding into the brain, eyes and ears have been seen rarely (affecting less than 1 in 1,000 patients taking Angiox). Bleeding events may be severe and result in other uncommon complications, such as haematoma or anaemia. If the bleeding is severe enough, blood transfusions may be necessary, and in rare cases even death may be the result.

The following risks are uncommon (>=1/1,000 to <=1/100):
-Thrombocytopenia, Anaemia, Hypersensitivity (including anaphylactic reaction and shock), headache, nausea and lower blood pressure.
The following risks are rare (>=1/100 to <1/10):
Thrombosis (blood clots), which may result in serious or fatal complications such as heart attack and chest pain; changes in heart beats; back pain, shortness of breath.

Benefits for the patient: if it turns out that bivalirudin is safer and / or more effective than UFH, the standard treatment that the patient may have received, the patient may benefit from it. It is also possible that the patient himself does not directly benefit from participation in the study, but other people in the future who will have a TAVR will benefit from the information collected during this study.

Contacts

Public
Medicines Company

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Scientific
Medicines Company

Talstrasse 59
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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. >= 18 years of age
2. High risk (Euroscore >=18, or considered inoperable) for surgical aortic valve replacement;
3. Undergoing TAVR via transfemoral arterial access;
4. Provide written informed consent before initiation of any study related procedures

Exclusion criteria

Patients will be excluded from the study if any of the following exclusion criteria apply prior to enrollment:
1. Any known contra-indication to the use of bivalirudin (except presence of severe renal impairment [GFR<30 ml/min] since these patients will be included in the trial - please see protocol section 8.1.1) or
2. Refusal to receive blood transfusion
3. Mechanical valve (any location) or mitral bioprosthetic valve
4. Extensive calcification of the common femoral artery, or minimal luminal diameter <6.5 mm
5. Use of elective surgical cut-down for transfemoral access;
6. Concurrent performance of percutaneous coronary intervention with TAVR
7. International normalized ratio (INR) >= 2 on the day of TAVR procedure, or known history of bleeding diathesis
8. History of hemorrhagic stroke, intracranial hemorrhage, intracerebral mass or aneurysm, or arteriovenous malformation
9. Severe left ventricular dysfunction (left ventricular ejection fraction<15%)

10. Severe aortic regurgitation or mitral regurgitation (4+);
11. Hemodynamic instability (e.g. requiring inotropic or IABP support) within 2 hours of the procedure;
12. Dialysis dependent;
13. Administration of thrombolytics, glycoprotein IIb/IIIa inhibitors, or warfarin in the 3 days prior to the procedure;
14. Acute myocardial infarction, major surgery or any therapeutic cardiac procedure (other than balloon aortic valvuloplasty) within 30 days
15. Percutaneous coronary intervention within 30 days
16. Upper gastrointestinal or genitourinary bleed within 30 days
17. Stroke or transient ischemic attack within 30 days
18. Any surgery or biopsy within 2 weeks
19. Administration of: a. UFH within 30 minutes of the procedure, b. Enoxaparin within 8 hours of the procedure c. Fondaparinux or other LMWHs within 24 hours of the procedure d. Dabigatran, rivaroxaban or other oral anti-Xa or antithrombin agent within 48 hours of the procedure e. Thrombolytics, GPI, or warfarin within 72 hours of the procedure
20. Absolute contraindications or allergy that cannot be pre-medicated to iodinated contrast
21. Contraindications or allergy to aspirin or clopidogrel
22. Known or suspected pregnant women, or nursing mothers. Women of child-bearing potential will be asked if they are pregnant and will be tested for pregnancy.
23. Previous enrolment in this study
24. Treatment with other investigational drugs or devices within the 30 days preceding enrollment or planned use of other investigational drugs or devices before the primary endpoint of this study has been reached.;Patients excluded for any of the above reasons may be re-screened for participation at any time if the exclusion characteristic has changed.

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):	12-12-2012
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Angiox
Generic name:	Bivalirudin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-06-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-02-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-04-2013
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-11-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	27-02-2015
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	EUCTR2012-000632-26-NL
ClinicalTrials.gov	NCT01651780andNTR3533
CCMO	NL41130.100.12