Bivalirudin Infusion for Ventricular Infarction Limitation

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

Summary

ID

NL-OMON41679

Source
ToetsingOnline

Brief title
BIVAL

Condition

- Myocardial disorders

Synonym
Heart Attack, Ventricular Infarction

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bivalirudin, PCI, Ventricular Infarct

Outcome measures

Primary outcome

The primary end point is infarct size assessed by CMR 5 days post-PPCI.

Secondary outcome

The secondary endpoints of this trial are:

* CMR micro-vascular obstruction (MVO) assessment at 5 days

* CMR myocardial salvage index (MSI) at 5 days

* CMR assessment of LVEF at 5 days

* CMR assessment of LVEF at 90 days

* TIMI flow and MBG at end of PPCI

* In-hospital NACE up to 5 days or discharge, whichever comes first (death,

re-infarction, ischaemia driven revascularisation (IDR) and Bleeding Academic

Research Consortium (BARC) *3 bleeding)

* Death at 90 days

Study description

Background summary

The BIVAL study is a multicenter, multinational, prospective, open-label, randomized controlled, phase IIIb trial. The objective of this study is to determine whether bivalirudin, compared to unfractionated heparin (UFH), for primary percutaneous coronary intervention (PPCI) in large ST-segment elevation myocardial infarction (STEMI) can reduce infarct size.

Study objective

The study hypothesis is that anticoagulation with bivalirudin for primary PCI in STEMI subjects with a 4 h infusion post-PCI will reduce infarct size compared with anticoagulation with UFH as assessed by CMR 5 days after the index event.
The primary objective of this study is to determine the effect on infarct size of bivalirudin infusion for the duration of PPCI and for 4 hours after the procedure compared to UFH in PPCI.
The study will also investigate whether according to the two study treatments there are any observed differences in the degree of successful mechanical reperfusion or biomarkers of injury that may account for any observed difference in infarct size, LVEF, safety and efficacy.

Study design

This study will be a multi-center, multinational, open-label, randomized controlled trial in subjects undergoing PPCI for a large acute myocardial infarction. The definition for a sizable infarction is outlined in Appendix 1 of the protocol, and consists of a simplified angiographic scoring system based on the extent of myocardium in jeopardy according to the location of the occlusion. A total of approximately 200 subjects will be included and randomized. Subjects will be stratified prior to randomization according to: a) total duration of ischemic pain (<6 h vs. *6 h) and (b) site. Informed consent will be obtained from subjects meeting the inclusion criteria before the initiation of any study-specific procedures.
All clinical endpoints of the trial will be investigator reported and captured in the electronic case report form (eCRF) and the primary endpoint will be evaluated by a blinded core lab with no access to treatment information or clinical data.

Subjects will be consented for the study prior to angiography, but will only be enrolled and randomized in the study after eligibility confirmation through angiography in the cardiac catheterization laboratory (CCL). All subjects will receive aspirin and a loading dose of any approved P2Y12 inhibitor (unless already on maintenance dose), as soon as logistically feasible following first medical contact. The use of bivalirudin prior to randomisation is prohibited. The use of enoxaparin prior to randomization is also prohibited. The use of UFH prior to randomization is according to institutional practice and is neither encouraged nor discouraged by the study protocol and will be documented in the eCRF. Among subjects treated by radial access, which inevitably will occur prior to randomization, UFH may be given to those who have not received any UFH earlier, but re-administration of UFH to subjects who had already received a bolus in the pre-hospital setting is prohibited.
Following coronary angiography and if:
1) TIMI 0 or 1 is present in the IRA and
2) The angiographic criteria for a large myocardial infarction are fulfilled (Appendix 1 of the protocol), and
3) a decision is made to proceed to PPCI,

then subjects will be randomly assigned 1:1, to receive either bivalirudin or UFH (control) in an open-label fashion. Randomization will be stratified by: (a) duration of symptom onset to randomization (<6 h versus *6 h) and (b) site.

Intervention

At baseline, post-PCI, end of 4 hour infusion, and at 12-24 h post-PPCI measurements of study biomarkers (micro-particle release, thrombin-anti-thrombin complexes [TAT], myeloperoxidase [MPO]) will be collected.
Next to that two CMRs will be performed to check the infarct size and to assess LVEF, that are not in all sites standard of care. One at 5 days and one at 90 days post randomization.

Study burden and risks

Most procedures are performed as per standard physician*s practice for subjects going for a PPCI.
Study specific procedures for the subject (this is additional to all standard physician*s practice (ECGs, and other (blood) sampling or procedures)): -ICF procedure -2 CMRs, -Blood sampling for study biomarkers.

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.
There is a risk of minor discomfort, bruising, bleeding, swelling, or (rarely) infection at the site of needle insertion for blood drawing and intravenous infusion.

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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients may be included in the study if they meet all of the following criteria:;
1.* 18 years;
2.Experience ischemic symptoms of >20 min and <12 h and have a diagnosis of STEMI with ST segment elevation of *1 mm in *2 contiguous precordial leads, or presumably new left bundle branch block;
3. Provide written informed consent (or witnessed consent in countries and sites where such patient consenting is applicable) before initiation of any study related procedures;
4. Have TIMI 0 or 1 flow in the IRA on initial angiogram;
5. Fulfill angiographic criteria/score for a large infarction based on initial angiogram (APPROACH score of *21) ;
6. Are candidates for PPCI;
7. Administration of an initial dose of 150-325 mg orally (or 250-500 mg IV) and a loading

dose of any approved P2Y12 inhibitor

Exclusion criteria

Patients will be excluded from the study if any of the following exclusion criteria apply prior to enrollment;
1. Contraindication or known hypersensitivity to bivalirudin or UFH;
2. Refusal to receive blood transfusion/products;
3. Subjects requiring staged coronary artery bypass graft (CABG) procedure within the first 90 days;
4. Known international normalized ratio (INR) * 2 or known prothrombin time (PT) >1.5 times upper limit of normal on the day of the index PPCI, or known history of bleeding diathesis
5. Therapy with vitamin K antagonists (VKA), within 72 h of PPCI
6. Therapy with dabigatran, rivaroxaban or other oral anti-Xa or antithrombin agents within 48 h of PPCI
7. History of hemorrhagic stroke, intracranial hemorrhage, intracerebral mass, aneurysm, arteriovenous malformation, or recent head injury (within the last 5 days)
8. Subjects with previous history of Q-wave MI
9. Known glomerular filtration rate (GFR) <30 milliliter (mL)/minute (min) or dialysis dependent
10. Major surgery within the previous 30 days
11. Minor surgery/biopsy exclusions in the past 3 days
12. Upper gastrointestinal or genitourinary bleed 30 days prior to randomisation
13. Stroke or transient ischemic attack 30 days prior to randomisation
14. Administration of thrombolytics or GPI 72 h prior to PPCI
15. Administration of enoxaparin 8 h prior to PPCI
16. Administration of bivalirudin 12 h prior to PPCI
17. Administration of fondaparinux or other LMWH 24 h prior to PPCI
18. Known contraindications to aspirin or P2Y12 inhibitor
19. Known allergy that cannot be pre-medicated to iodinated contrast
20. Known contraindication to CMR
21. Women of child bearing potential (1)
22. Previous enrolment in this study
23. Treatment with other investigational drugs or devices within the 30 days preceding enrolment or planned use of other investigational drugs or devices before the primary endpoint of this study has been reached
24. Patients with a body wieght > 150 kg;(1) Child bearing potential is defined as:
A female patient is considered to have childbearing potential unless she meets at least one of the following criteria:
* Age *50 years and naturally amenorrhoeic for * 1 year*
* Premature ovarian failure confirmed by a specialist gynaecologist;
* Previous bilateral salpingo-oophorectomy, or hysterectomy.
* XY genotype, Turner*s syndrome, uterine agenesis;
*Amenorrhoea following cancer therapy does not rule out childbearing potential

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):	09-12-2014
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:	27-02-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2014
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-11-2015
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	EUCTR2012-002314-39-NL
CCMO	NL47484.078.14