European Ambulance Acute Coronary Syndrome Angiox Trial: EUROMAX

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

Summary

ID

NL-OMON38053

Source
ToetsingOnline

Brief title
EUROMAX

Condition

- Coronary artery disorders

Synonym
heart attack, ST segment elevation acute coronary syndrome (ST-ACS)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ambulance service, bivalirudin, primary percutaneous coronary intervention (PCI), ST segment elevation acute coronary syndrome (STE-ACS)

Outcome measures

Primary outcome

Primary Endpoint at 30 days:

• A composite of death and non-CABG-related protocol major bleeding

Secondary outcome

• Death or re-infarction (MI) at 30 days

• Death at 30 days and 365 days

• Re-infarction (MI) at 30 days

• IDR at 30 days

• Death, re-infarction (MI) or IDR at 30 days

• Death, re-infarction (MI) or non-CABG-related protocol major bleeding at 30

days

• Major bleeding at 30 days (protocol, TIMI and GUSTO)

• Minor bleeding at 30 days (protocol, TIMI, and GUSTO)

• Incidence of thrombocytopenia post index procedure and at 30 days

• Stent thrombosis (ARC definition) at 30 days

• Stroke at 30 days

Sub-Analysis:

• ST segment resolution sub-analysis (Appendix 04)

Study description

Background summary

Randomised clinical studies have confirmed primary coronary intervention to be the ideal therapy for patients with ST segment elevation acute coronary syndrome. Rapid diagnosis of the clinical symptom complex, initiation of an antithrombotic treatment based on acetylsalicylic acid, clopidogrel and unfractioned heparin, rapid transport of the patient to a cardiac cath lab to carry out a diagnostic coronary angiography and the subsequent therapy depending on the diagnosis in line with current European guidelines, are essential to ensure long-term success of the treatment. Early use of anti-coagulants, known as thrombin inhibitors, that prevent the development and activation of thrombin, , has been proven to be capable of preventing thromboembolic complications, particularly with the concomitant use of platelet aggregation inhibitors. The thrombin inhibitor bivalirudin, under the trade name of Angiox®, is authorized throughout Europe for the treatment of patients with acute coronary syndrome (instable angina pectoris and non-ST segment elevation acute coronary syndrome), who are suitable for early coronary intervention, and also as an intravenous anticoagulant during percutaneous coronary intervention. In the HORIZONS AMI study, involving over 3,600 study patients with ST segment elevation acute coronary syndrome, bivalirudin was compared with a standard therapy of unfractioned heparin and GP IIa/IIIb inhibitors and was shown to be safe with the same level of efficacy (p=0.006 for "net adverse clinical outcomes"). In this EUROMAX study, the efficacy and safety of early administration of bivalirudin is to be tested, starting while the patient with ST segment elevation acute coronary syndrome is transferred to the cardiac cath lab. The study objective is to test if early administration of bivalirudin in patients with ST segment elevation acute coronary syndrome results in a better 30 day treatment outcome than the current standard therapy of unfractioned heparin with or without a GP IIa/IIIb inhibitor. EUROMAX is a European, multi-centre, multi-national, prospective, randomised, open-label, phase IIB study, with a planned study population of 3680.

Study objective

The purpose of the trial is to show that the early administration of bivalirudin improves 30 day outcomes when compared to the current standard of care in patients with STE-ACS, with an onset of symptoms of >20 minutes and <12 hours, intended for a primary PCI management strategy, presenting either via ambulance or to centres where PCI is not performed.

Study design

Multi-centre, multi-national, prospective, randomised, open-label, comparison

of bivalirudin to other guideline based current therapies (excluding bivalirudin).

Intervention

Patients who have had symptoms of an ST segment elevation acute coronary syndrome for more than 20 minutes within the last 12 hours, who are to be transferred to a suitably equipped clinic for primary coronary intervention, are informed about the study and once they have given their written consent are randomized in a ratio of 1:1 into either the treatment with bivalirudin or the corresponding standard therapy.

All patients also receive acetylsalicylic acid for at least one year and a P2Y12 receptor blocker in accordance with standard clinical practice. The treatment with bivalirudin is continued during the diagnostic coronary angiography and, if primary coronary intervention is required, up to 4 hours after the end of the procedure. If no coronary intervention is carried out, the Bivalirudin administration is continued at a low dose for up to 72 hours, at the study investigator's discretion. The dose and treatment term in the standard therapy control arm correspond to the routine requirements in line with European guidelines. The patients otherwise receive the standard therapy for the treatment of an ST segment elevation acute coronary syndrome. If a patient meets the study inclusion criteria, the study will be explained to him in the ambulance or the primary hospital and he will be asked to sign the written informed consent declaration. The patients are then randomized and will receive the assigned study medication. On arrival in the cardiac cath lab the diagnostic coronary angiography and if necessary in the same session the coronary intervention can be carried out as planned, according to standard clinic routine. Participation in the study will not extend the patient's in-patient hospital stay. All patients are regularly clinically monitored during their stay in the clinic. Further follow-up check-ups are carried out after 30 days and after one year.
In the context of this study a total of 75 ml at 5 timepoints are drawn from each patient.

Study burden and risks

Angiox® has been used in over two million patients to date. It is, however, possible that not all side effects and risks of Angiox® have been investigated. One common side effect of the treatment with bivalirudin (occurring in more than 1 in 10 patients) is bleeding; this can occur anywhere in the body and can cause the following complications: anaemia (low red blood cell count), haematoma (a collection of blood outside the vessels), bleeding and bruising at the injection site and a lower platelet count (thrombocytopenia). Blood coagulation can also be affected. In rare cases (in fewer than one in 1,000 patients) bleeding can lead to death or to irreversible disability. The risk of

bleeding is increased if Angiox® is used concomitantly with other blood thinning drugs, and in some 3% of cases (3 in 100 patients) blood or blood product transfusion are required. One common undesirable event (occurring in one to ten in 100 patients) is the formation of a blood clot (thrombosis), that can lead to severe or fatal complications, such as a heart attack. An allergic reaction to Angiox® is also possible. This can manifest in the form of a rash (hives), itching all over the body or shortness of breath. These are rare side effects (one in 1,000 to one in 100 patients) that can be very serious or even fatal. These include headache, change in blood pressure, change in the heart rate, nausea and/or vomiting, backache, thoracic pain, shortness of breath, rash. The most common side effect in the control arm of the study with the use of heparin is bleeding. This can be at the injection site, in the stool, in the urine or any other part of the body. Another possible side effect is the tendency to haematomas. Bleeding in the brain and heparin-induced thrombocytopenia (fall in the blood platelet count) have also been observed. At the sites where blood is taken pain, burning, swelling, bleeding, blood clots, pallor and rarely inflammation or nerve damage can occur. Overall, no more than 75 ml of blood will be drawn from each patient during the course of the study. Pregnant or breastfeeding women are not allowed to take part in the study. As with any medication rare, previously unobserved side effects can occur. The patient is monitored for side effects, and given the appropriate treatment if problems arise. It is also necessary for the patient to inform the study investigator about any health problems or health impairment or if he is feeling generally unwell or there is a change in the treatment during the trial, even if it does not appear to be likely that it is connected to receiving the study preparation. The study doctor will decide on suitable measures to take. An independent expert group will also constantly monitor the safety of the study and side effects of the study medication during study participation and for the entire study duration. It is possible that early administration of Angiox® (bivalirudin) can inhibit bleeding more safely and with better patient tolerance than heparin. While it cannot be guaranteed that the patient will benefit from taking part in this study, the experience gained may be very beneficial for future patients with a heart attack.

Contacts

Public
Medicines Company

115L Milton Park, Abingdon
Oxfordshire, OX14 4SA
GB
Scientific
Medicines Company

115L Milton Park, Abingdon
Oxfordshire, OX14 4SA
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects may be included in the study if they present either via ambulance or to a centre where PCI is not performed and meet all of the following criteria:
1. Provide written informed consent before initiation of any study related procedures. Patients randomised in the ambulance may initially sign an abridged version.
2. Be aged >=18 years at the time of randomisation.
3. Have a presumed diagnosis of a STE-ACS with onset of symptoms of >20 minutes and <12 hours with one or more of the following: ST segment elevation of >=1 mm in >=2 contiguous leads Presumably new left bundle branch block An infero-lateral MI with ST segment depression of >=1 mm in >=2 of leads V1-3) with a positive terminal T wave
4. All patients must be scheduled for angiography +/- PCI (if indicated) <2 hours after first medical contact

Exclusion criteria

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomisation:
1. Any bleeding diathesis or severe haematological disease or history of intra-cerebral mass, aneurysm, arterio-venous malformation, haemorrhagic stroke, intra-cranial haemorrhage or gastrointestinal or genitourinary bleeding within the last 2-weeks.
2. Patients who have undergone recent surgery (including biopsy) within the last two weeks.
3. Patients on warfarin (not applicable if INR known to be <1.5).
4. Patients who have received UFH, LMWH or bivalirudin immediately before randomisation.
5. Thrombolytic therapy within the last 48 hours.

6. Absolute contraindications or allergy that cannot be pre-medicated to iodinated contrast or to any of the study medications including aspirin or clopidogrel.
7. Contraindications to angiography, including but not limited to severe peripheral vascular disease.
8. If it is known pregnant or nursing mothers. Women of child-bearing age will be asked if they are pregnant or think that they may be pregnant.
9. If it is known a creatinine clearance <30 mL/min or dialysis dependent.
10. Previous enrolment in this study.
11. Treatment with other investigational drugs or devices within the 30 days preceding randomisation or planned use of other investigational drugs or devices in this trial.
12. Patients may not be enrolled if the duration of randomised investigational medicinal product (IMP) anti-thrombin infusion is likely to be less than 30 minutes from the time of onset to the commencement of angiography.
13. Patients may not be enrolled within a primary PCI capable hospital (unless at the time of randomisation the catheter laboratory is not available and the patient requires transfer to another primary PCI capable hospital).
14. Estimated body weight of >120 kg.

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):	05-11-2010
Enrollment:	800
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	23-02-2010
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	31-05-2010
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	15-06-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	25-10-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	14-06-2012
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	28-08-2012
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2008-007290-20-NL
ClinicalTrials.gov	NCT01087723
CCMO	NL31565.075.10