A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects with a Recent Acute Coronary Syndrome

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

Summary

ID

NL-OMON33722

Source
ToetsingOnline

Brief title
The ATLAS ACS 2 TIMI 51 Trial

Condition

- Coronary artery disorders

Synonym
Acute Coronary Syndrome, Heart Infarction

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: De opdrachtgever van het onderzoek

Intervention

Keyword: anti-Xa, cardiovascular, efficacy, Rivaroxaban

Outcome measures

Primary outcome

The primary objective of the study is to determine whether rivaroxaban in addition to standard care reduces the risk of the composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke in subjects with a recent ACS compared with placebo in addition to standard care.

Secondary outcome

* Evaluation of secundary efficacy endpoints (composites of all cause death, MI, stroke, recurrent ischemia requiring revascularisation and/or hospitalisation)

* To examine the effect of rivaroxaban on net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or a Thrombolysis in Myocardial Infarction (TIMI) major bleeding event not associated with coronary artery bypass graft (CABG) surgery

* Evaluation of safety of rivaroxaban (bleeding risk)

* Evaluation of (patient completed) health questionnaires as well as evaluation of medical resource utilization.

Study description

Background summary

Heart and blood vessel disease is one of the major causes of death in the western world. After having a myocardial infarction and unstable angina (pain on the chest in rest), anti-coagulant medication is prescribed (*bloodthinners*) to prevent the formation of new bloodclots which can block the (coronary) arteries again. The coronary arteries are the vessels which transport blood to the heart.
Aspirin is one of the most prescribed medications after a myocardial infarction and unstable angina. Besides aspirin a number of other blood thinners is prescribed with different modes of action (eg. thienopyridines). Often, combinations of blood thinners are prescribed.
Rivaroxaban is a member of the category of factor Xa inhibitors (factor Xa plays a part in blood clotting). In this trial it will be investigated whether rivaroxaban can make a substantial contribution to the prevention of new myocardial infarctions, cardiovascular death or strokes when it is given in combination with aspirin alone or in combination with aspirin and a thienopyridine.

Study objective

The primary objective of the study is to determine whether rivaroxaban in addition to standard care reduces the risk of the composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke in subjects with a recent ACS compared with placebo in addition to standard care.

Study design

This is an international, randomized, multicenter, double-blind, placebo-controlled, event-driven study designed to evaluate the safety and efficacy of rivaroxaban in subjects with recent ACS (STEMI, NSTEMI, or UA) who are receiving background low dose aspirin therapy (Stratum 1, aspirin only) or with thienopyridine therapy (Stratum 2, aspirin plus a thienopyridine).

Each phase has a screening/baseline phase within the 6 days prior to randomisation or on the day of randomisation (day 1). The double-blind treatment period lasts for a maximum of 36 months, with an endvisit planned at the end of this period or at the time a patient will leave the trial prematurely. Approximately 30 days after the last dose of study drug, a posttreatment follow-up visit will occur and will include assessment of any new adverse events and follow-up of any ongoing adverse events. The total duration of the study will be approximately 36 months and can be stopped prematurely if enough endpoints are collected (983 primary efficacy endpoints in both strata,

of which at least 728 in stratum 2).

Per stratum there are always 3 treatment groups: placebo, rivaroxaban in a twice daily dose (5 mg) and rivaroxaban in a twice daily dose (2,5 mg). See also page 41 of the protocol for a schematic overview. Patients will be randomized with a chance of 1 in 3 to one of the 3 treatment groups.

Intervention

In both strata patients receive ór placebo, ór rivaroxaban in a twice daily dose (5 mg), ór rivaroxaban in a twice daily dose (2,5mg).

Study burden and risks

Burden to the patient: patients will be for a maximum of 36 months in the trial. After discharge from the hospital, patients need to visit the hospital for trial visits for several times (depending on when they started with the trial) and will undergo a number of trial procedures (a.o. blooddrawings and completion of questionnaires).
Risks: the side effects of aspirin and thienopyridines are known.
In earlier trials with healthy volunteers no differences were seen in the incidence of mild side effects between subjects treated with rivaroxaban and subjects treated with placebo.
Side effects which were reported in more than 3% of trialpatients were headache, pain in one of the extremities, diarrhea, swelling in one of the extremities, nausea, constipation, sleeplessness, urinary tract infection, fever, itching, fatigue and sore throat. Liverenzyme abnormalities were reported. Rivaroxaban is a bloodthinner which can make it more difficult for the blood to clot in case of a bleeding. Therefore, there is a risk of a bleeding. The patient will get an extensive screening vist, before the patient will be randomized. During the trial, the patient will be followed closely. In case of side effects, extra visits will be planned to follow up the patient. In case of bleeding and liver abnormalities, the guidelines on page 61-65 of the protocol are given.
Risks of blooddrawing are minimal.

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

Potential subjects must satisfy the following criteria to be enrolled in the study:
* Man or woman 18 years of age or older
* Currently receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine per national dosing recommendation)
* Have been hospitalized for symptoms suggestive of ACS that lasted at least 10 minutes at rest, and occurred 48 hours or less before hospital presentation and have a diagnosis of:
* STEMI:
elevation of ST-segment more than 0.1 millivolt (mV) in 2 or more continuous ECG leads, or new left bundle branch block, or ST segment depression 0.1 mV or greater in 2 of the precordial leads V1-V4 with evidence suggestive of true posterior infarction, all with elevated biomarkers of myocardial necrosis (creatinine kinase muscle and brain isoenzyme [CK-MB] or troponin)
* NSTEMI:
Transient ST-segment elevation, or ST-segment depression, or T-wave changes consistent with myocardial ischemia along with elevated biomarkers of myocardial necrosis (creatinine kinase-muscle and brain isoenzyme [CK-MB] or troponin)
* UA with at least 1 of the following:
* transient or persistent ST-segment deviation 0.1 mV or greater in 1 or more ECG leads
* TIMI risk score *3.
* Subjects who are 18 to 54 years of age inclusive must also have either diabetes mellitus or a prior MI in addition to the presenting ACS event.

* Women must be:
* postmenopausal (for at least 2 years), or
* surgically sterile, (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
* abstinent (at the discretion of the investigator/per local regulations), or
* if sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method, male partner sterilization) as local regulations permit, before entry, and must agree to continue to use the same method of contraception throughout the study.
* Women of childbearing potential must have a negative urine *-human chorionic gonadotropin (*-hCG) pregnancy test at screening. Serum pregnancy testing may be performed if required by local regulation.
* Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

Exclusion criteria

- conditions that may increase the risk of bleeding
- severe concomitant diseases
- required drugs which are not allowed acc. to the protocol (eg. need for continued treatment with anticoagulant drugs, treatment with strong CYP 3A4 and P-gp inhibitors)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	28-01-2009
Enrollment:	225
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rivaroxaban
Generic name:	Rivaroxaban

Ethics review

Approved WMO Application type:	First submission
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	EUCTR2008-002708-25-NL
CCMO	NL25257.060.08