An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention.

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Dual Primary Objectives:* To determine if apixaban is noninferior to VKA (INR target range 2.0-3.0) on the combined endpoint of ISTHmajor or clinically relevant non-major bleeding in patients with NVAF who develop ACS or undergo PCI withplanned…

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

Summary

ID

NL-OMON47141

Source
ToetsingOnline

Brief title
CV185316 - Augustus

Condition

- Other condition
- Cardiac disorders, signs and symptoms NEC

Synonym
Coronary stent placement, Fibrillation of the muscles of the atria of the heart, Heart attack

Health condition

bloedingen

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Bristol-Myers Squibb,farmaceutische industrie

Intervention

Keyword: Apixaban, Atrial Fibrillation and Acute, Coronary Syndrome, Percutaneous Coronary Intervention, Warfarin and Aspirin

Outcome measures

Primary outcome

Primary endpoints (safety):

The primary endpoint for apixaban versus VKA is

* ISTH major or CRNM bleeding

The primary endpoint for aspirin versus placebo is

* ISTH major or CRNM bleeding

Secondary outcome

Secondary endpoints:

The secondary endpoint for apixaban versus VKA includes

* Superiority on major or CRNM bleeding

* Superiority for the composite of all-cause death/all-cause

rehospitalization.

*The composite endpoints of death, stroke, myocardial infarction, stent

thrombosis, urgent coronaire revascularization

* First re-hospitalization for any cause

The secondary endpoint for aspirin versus placebo includes

* The composite endpoints of death, stroke, myocardial infarction, stent

thrombosis, urgent coronaire revascularization

* First re-hospitalization for any cause

Study description

Background summary

Non-Valvular Atrial Fibrillation (AF) is a disease that causes the upper chambers of the heart to quiver rather than contract normally. AF may cause blood clots to form in the heart. When blood clots form in the blood vessels, they can be dangerous because they can block the circulation. When blood clots form in the arteries or heart, they stop the flow of blood. This can cause a heart attack. If a blood clot clogs the blood vessels in the brain, this can cause a stroke. A stroke is a condition where the brain can lose function, cause serious disability, or cause death. In order to break down or prevent clot formation in patients with AF, a blood thinner, such as Vitamin K Antagonist (VKA) or other anticoagulant, such as apixaban, is commonly used.

The standard treatment to break down or prevent blood clots in patients with ACS or a recent PCI is known as *Dual Antiplatelet Therapy* and is not effective in breaking down clots related to AF.

The optimal treatment for patients with a current or history of AF and recent ACS or PCI is not known at this time. Risk of bleeding is present with any blood thinner. The combination of certain treatments can lead to increased risk of bleeding. This study is being conducted to determine if apixaban is safer than the blood thinner Warfarin in subjects with non-valvular AF and ACS or PCI in relation to bleeding. In the Netherlands, Warfarin is not registered as medication.

This study will also evaluate if treatment with apixaban or the oral VKA drug called Warfarin and a P2Y12 inhibitor alone is safer than treatment of apixaban

or Warfarin with a combination of a P2Y12 inhibitor and Aspirin.

Study objective

Dual Primary Objectives:
* To determine if apixaban is noninferior to VKA (INR target range 2.0-3.0) on the combined endpoint of ISTH
major or clinically relevant non-major bleeding in patients with NVAF who develop ACS or undergo PCI with
planned concomitant P2Y12 inhibitor therapy.
* To determine if anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor is superior to anticoagulant
plus dual antiplatelet therapy with a P2Y12 inhibitor and aspirin on the combined outcome of ISTH major or
clinically relevant non-major bleeding in patients with NVAF who develop ACS or undergo PCI with planned
concomitant P2Y12 inhibitor therapy.

Secondary Objectives:
To compare apixaban and VKA (with concomitant P2Y12 inhibitor therapy), in patients with NVAF who develop
ACS or undergo PCI, with respect to:
Superiority on ISTH major or clinically relevant non-major (CRNM) bleeding
* The composite of all-cause death and all-cause rehospitalization.
* Death, stroke, myocardial infarction, stent thrombosis, or urgent coronary revascularization
*

To compare aspirin and aspirin placebo (with concomitant P2Y12 inhibitor therapy), in patients with NVAF who
develop ACS or undergo PCI with respect to:
The composite of all-cause death and all-cause rehospitalization.
* Death, stroke, myocardial infarction, stent thrombosis, or urgent coronary revascularization
*

Study design

Patients with a recent ACS or undergoing PCI with NVAF and planned treatment with P2Y12 inhibitor and oral
anticoagulation for at least 6 months will be evaluated for eligibility during their ACS or post-PCI hospitalization.
Randomization can be performed up to 14 days after the ACS or PCI and should take place as early as possible after
cessation of parenteral anticoagulant and when clinically stable. Both patients with and without prior oral

anticoagulant treatment can be included in this trial. Patients who are on a VKA prior to randomization will have
VKA discontinued and will not be dosed with apixaban for 4 days or until the INR is less than 2.0. At the time of
enrollment, each patient who meets inclusion / exclusion criteria will be randomized via IVRS using a 2 x 2 factorial
design to either apixaban or VKA and to either aspirin or aspirin placebo. Randomization will be stratified by
indication at enrollment (ACS vs. PCI).
Overall, the trial will include approximately 1/3 of patients with a recent ACS.

Intervention

4 treatment groups:
Apixaban and aspirin
Warfarin and aspirin
Apixaban and aspirin placebo
Warfarin and aspirin placebo

Study burden and risks

please refer to protocol section 5.1 'Flow Chart/Time and Events Schedule' for a complete overview of study procedures that will be done.

Apixaban:

Like all medicines, apixaban can cause side effects.
* Bleeding in the eye, under the skin, or from the nose and gums
* Bruising
* Vomiting of blood
* Blood in stool and urine

Uncommon Side Effects (between one in a hundred to one in a thousand might experience the event)
* Sensitivity reaction (e.g. skin rash, difficulty breathing, swelling of the face)
* Bleeding in the brain, in the lining of the stomach, from the mouth, and from haemorrhoids (piles)
* Blood in sputum
* Abnormal bleeding from injection sites, sites of cuts or injuries, or vaginal bleeding
Rare (between one in a thousand to one in ten-thousand)
* Bleeding in the respiratory tract (including the lungs)

VKA (including Warfarin, the drug that will be used in this trial)

Like all medicines, VKA Warfarin can cause side effects.
* Bleeding in the brain, under the skin, in the chest cavity, in or from digestive tract, or from the nose
* Blood in the stool or urine
* Vomiting of blood
* Abnormal bleeding from injection sites, sites of cuts or injuries, or vaginal bleeding
* Sensitivity reaction (e.g. skin rash, difficulty breathing, swelling of the face)
* Fever, diarrhea, vomiting feeling and being sick
* Skin rashes
* Abdominal pain, bloating
* Liver enzyme changes
* Jaundice (yellowing of the skin and white of eyes)
The risk of bleeding or bruising while on a VKA Warfarin is related to the intensity and duration of the blood thinning effect, and must be monitored regularly with blood tests (INR monitoring).

Aspirin
Aspirin has many uses, but for the purpose of this study is being used as an antiplatelet medication (helps to prevent blood*s clotting). Like all medicines, Aspirin can cause side effects. Taking aspirin can increase risk of bleeding.
* Gastrointestinal (stomach) bleeding/Ulcer
* Sensitivity reaction (e.g. skin rash, difficulty breathing/asthma, swelling under your skin)
* Abdominal pain
* Heartburn
* Nausea
* Tinnitus or *ringing in the ears*

In addition VKAs and/or Aspirin can interact with numerous prescription and over-the-counter medicines and herbal and botanical (natural) products, as well as different foods.

Other Potential Risks
Assigned study treatment may not prevent blood clots from forming. It is possible a blood clot can form and lead to a heart attack, stroke or even death.

When study medications are taken alone or in combination with other medications, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening.

When a sample of your blood is drawn, patient may experience some temporary discomfort, faintness, inflammation of the vein, bruising, bleeding swelling

and/or, in rare circumstances, infection at the needle site.

Reproductive risks
Women: Study treatments may affect an unborn child or nursing infant.

Men: It is not known if the study treatment may affect sperm or an unborn child.

Contacts

Public
Bristol-Myers Squibb

Parc de l'Alliance - Avenue de Finlande 4
Braine-l'Alleud 1420
BE
Scientific
Bristol-Myers Squibb

Parc de l'Alliance - Avenue de Finlande 4
Braine-l'Alleud 1420
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed Written Informed Consent
a) Subjects will be required to provide a written informed consent.
2. Target Population

a) Males and females 18 years of age (or age of majority) or older with either active or a history of non-valvular atrial fibrillation or flutter with the planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism for at least 6 months AND
b) An acute coronary syndrome (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI], or unstable angina), within
the prior 14 days with planned use of an approved P2Y12 inhibitor for at least 6 months
AND/OR
c)PCI (with or without stents) within the prior 14 days with planned use of an approved P2Y12 inhibitor for at least 6 months.
(If both an ACS event and an elective PCI occur within the same 14 day period, the investigator has the option to define the index event for the randomization to the interactive voice/web response system. It is recommended to choose the most recent event as the index event. However, for the
electronic case report form, if a patient has both an ACS and PCI within 14 days, both events can be selected.)
3. Subject Re-enrollment:
a) This study does permit the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (screen failure).

Exclusion criteria

- Conditions other than atrial fibrillation that require chronic anticoagulation (eg, prosthetic mechanical heart valve)
- Severe renal insufficiency (serum creatinine > 2.5 mg/dl [133 micromol/L] or a calculated creatinine clearance < 30 mL/min
- Patients with any history of intracranial hemorrhage
- Any contraindications to warfarin, apixaban, to intended P2Y12 inhibitors or to aspirin
- Patients who have or will undergo coronary arterial bypass graft (CABG) for their index ACS event
- Patients with known ongoing bleeding
- Patients with known coagulopathies

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-10-2017
Enrollment:	250
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Apixaban
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Aspirin
Generic name:	Aspirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Warfarin
Generic name:	Warfarin

Ethics review

Approved WMO Date:	05-09-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-07-2017
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2014-002004-24-NL
ClinicalTrials.gov	NCT02415400
CCMO	NL54023.056.16