A Multinational, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Ticagrelor twice daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Stroke in Patients with Type 2 Diabetes Mellitus

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON47716

Source
ToetsingOnline

Brief title
THEMIS

Condition

- Cardiac disorders, signs and symptoms NEC
- Diabetic complications
- Embolism and thrombosis

Synonym
cardiovascular risk, diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca BV

Intervention

Keyword: Cardiovascular death, Diabetes Mellitus, Intervention, Ticagrelor

Outcome measures

Primary outcome

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke (ischaemic, haemorrhagic or unknown etiology).

Secondary outcome

The secondary objectives of the study (presented in hierarchical order) are to compare the effect of long-term treatment with ticagrelor vs. placebo for:

1. Prevention of the composite of all-cause death, MI or stroke. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause death, MI or stroke

2. Prevention of CV death. The efficacy variable is time from randomisation to death of CV cause

3. Prevention of all-cause death. The efficacy variable is time from randomisation to death of any cause.

Study description

Background summary

Cardiovascular disease (CVD), which includes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease (PAD), is the leading cause of death in most developed countries. In the United States, CVD accounted for approximately 1 of every 3 deaths in 2009. The totality of evidence from basic research, clinical investigations, observational epidemiologic studies, and randomised clinical trials has provided strong support for the net benefits of acetylsalicylic acid (ASA)/AspirinTM in decreasing the risk of CVD events in a wide range of patients with established CHD. Diabetes substantially increases the risk of major cardiovascular (CV) complications in patients with and without established CVD (such that most patients with diabetes die of CV diseases.

Study objective

The overall safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo in patients with T2DM at high risk of CV events, with or without background low-dose ASA therapy. Bleeding events will be analyzed using the Thrombolysis in Myocardial Infarction Study Group (TIMI) definitions, those used in the PLATO (PLATelet inhibition and patient Outcomes) study, and the Bleeding Academic Research Consortium (BARC) definitions. Specific focus will be on:
* Time to first TIMI Major bleeding event (primary safety objective)
* Time to first TIMI Major or Minor bleeding event
* Time to first PLATO Major bleeding event
*Time to permanent discontinuation of study medication due to any bleeding event.
Non-serious AEs of interest (ie, dyspnoea, renal impairment, bradyarrhythmia, gout, and pneumonia), adverse events that leads to permanent discontinuation of study medication (DAEs) and all serious adverse events (SAEs) will be reviewed within the context of the earlier safety experience with the drug.

Study design

This is an event-driven, randomised, double blind, placebo controlled, parallel group, international multi-centre study to evaluate the effect of ticagrelor bd vs. placebo for prevention of major CV events in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke. Patients will be managed consistent with local standard of care including provision of dietary and lifestyle advice according to local diabetes treatment guidelines. Use of low-dose acetylsalicylic acid (ASA)/AspirinTM 75-150 mg once daily (od), is allowed if clinically indicated, as judged by the investigator.

Intervention

Patient will receive either ticagrelor bd orally or corresponding placebo.

Study burden and risks

The patient is asked to visit the site a maximum of 15 times and will receive a maximum of 12 telephone calls during the duration of the trial.
The patient will be asked to complete a questionaire 12 times max.
The patient will undergo a physical examination at the beginning of the trial and will have an electro cardiogram (ECG) at the randomisation visit.
Woman of childbearing potential have to provide a urine sample for a pregnancy test.
At the randomisation visit a blood sample will be taken after at least 6 hours of fasting.
The study medication may cause some side effects.
Taking of a blood sample may cause some discomfort.

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

1. Signed Informed Cosnent
2. Men or women *50 years of age
3. Diagnosed with T2DM defined by ongoing glucose lowering drug treatment prescribed by a physician for treatment of T2DM since at least 6 months prior to Visit 1
4. At high risk of CV events, defined as history of percutaneous coronary intervention or coronary artery bypass graft or angiographic evidence of * 50% lumen stenosis of at least 1 coronary artery

Exclusion criteria

1. Previous MI (with the exception of definite secondary MI [e.g., due to coronary revascularization procedure, profound hypotension, hypertensive emergency, tachycardia, or profound anaemia])
2. Previous stroke (transient ischaemic attacks [TIA] is not included in the stroke definition)
3. Planned use of ADP receptor antagonists (e.g., clopidogrel, ticlopidine, prasugrel), dipyridamole, or cilostazol. Planned use of ASA treatment at doses >150 mg od.;
4. Planned coronary, cerebrovascular, or peripheral arterial revascularization.;
5. Anticipated concomitant oral or intravenous therapy with strong cytochrome P450 3A4 (CYP3A4) inhibitors or CYP3A4 substrates with narrow therapeutic indices that cannot be stopped for the course of the study;
* Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin (but not erythromycin or azithromycin), nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir.;
* CYP3A4 substrates with narrow therapeutic index: quinidine, simvastatin at doses >40 mg daily or lovastatin at doses >40 mg daily;
6. Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses);
7. Patients with known bleeding diathesis or coagulation disorder, or with uncontrolled hypertension (defined as a systolic BP *180 mmHg and/or diastolic BP *100 mmHg);
8. History of previous intracerebral bleed at any time, gastrointestinal (GI) bleed within the past 6 months, or major surgery within 30 days;
9. Increased risk of bradycardic events (e.g., known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia) unless treated with a pacemaker;
10. Known severe liver disease (e.g., ascites and/or clinical signs of coagulopathy);
11. Renal failure requiring dialysis;

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:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-02-2014
Enrollment:	453
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Brilique
Generic name:	ticagrelor
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-12-2013
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-02-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	05-03-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-04-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-06-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	01-07-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-08-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	05-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2013-003519-23-NL
CCMO	NL46981.028.13