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Acarbose Cardiovascular Evaluation Trial

Submission date
03/11/2008

Recruitment status
No longer recruiting

Registration date
12/11/2008

Overall study status
Completed

Last Edited
02/11/2023

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The number of people worldwide diagnosed with diabetes is increasing rapidly every year. China has one of the highest rates of new onset type 2 diabetes (T2DM) in the world today. People with T2DM are at a greater risk of heart disease and stroke than the general population and have a reduced life expectancy. The purpose of the Acarbose Cardiovascular Evaluation (ACE) study is to determine if improving blood glucose control after meals using a drug called acarbose can reduce the risk of further heart disease or strokes in people who already have known heart disease. Acarbose is a licenced drug and is used worldwide for the treatment of diabetes. It is the most frequently prescribed treatment for diabetes in China. The study will also investigate whether this treatment can prevent or delay the onset of T2DM in people with above normal blood sugar levels who are at risk of developing diabetes. Approximately 6,500 patients will be recruited across China.

Who can participate?
Adults in China aged 50 years or older diagnosed with heart disease and who have an above normal blood sugar level.

What does the study involve?
The effectiveness of acarbose is being compared against a placebo. Each participant will receive either a 50mg acarbose tablet or a placebo three times a day.

What are the possible benefits and risks of participating?
Acarbose may help protect patients from developing heart related problems or strokes. It may also prevent or delay the development of T2DM. Taking the drug acarbose may cause some abdominal discomfort. Nausea has been reported with acarbose in <1% of patients, and in very rare cases (0.1%) acarbose may cause elevated liver enzyme levels. Taking blood samples at clinic visits may cause some discomfort and/or bruising or very rarely, a minor infection. The oral glucose tolerance test, which measures blood sugar levels before and after consumption of a sugary drink, may cause some nausea.

Where is the study run from?
The study is being sponsored and run by The University of Oxford, UK. It is being conducted in 176 hospitals in mainland China and Hong Kong. The participating hospitals are managed on a day-to-day basis through the University's office in Beijing.

When is the study starting and how long is it expected to run for?
December 2008 to April 2017.

Who is the main contact?
Professor Rury Holman
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Study website
http://www.dtu.ox.ac.uk/ace

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
NCT00829660

Secondary identifying numbers
11232

Study information

Scientific Title

The Acarbose Cardiovascular Evaluation (ACE) Trial: A long-term, multicentre, double-blind, randomised parallel-group trial to determine whether reducing post-prandial glycaemia can reduce cardiovascular-related morbidity and mortality in patients with established coronary heart disease or acute coronary syndrome who have impaired glucose tolerance

Acronym
ACE

Study objectives
To determine whether acarbose therapy can reduce cardiovascular-related morbidity and mortality in patients with impaired glucose intolerance (IGT) who have established coronary heart disease (CHD) or acute coronary syndrome (ACS). A secondary objective of the study is to determine if acarbose therapy can prevent or delay transition to type 2 diabetes mellitus (T2DM) in this patient population.

The first participant was enrolled on 17/02/2009 and randomised on 20/03/2009.

Please note that this trial was updated as of 02/03/2010, 21/09/2011 and 05/07/2017. All updates can be found in the relevant field with the above update date. Changes to the protocol were approved by OXTREC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxford Tropical Research Ethics Committee (OXTREC) on 28/10/2008 (ref: 51 08). Amendments to protocol were approved on the 17/02/2010. Further amendments to protocol approved on 18 /08/2011.
Added 01/08/2017: Amendments to the protocol were approved on the 17/02/2010, 18/08 /2011, 20/03/2012, 04/02/2014, 03/11/2015, 27/06/2016, 03/08/2016.

Study design
Phase IV multi-centre double-blind randomized controlled clinical outcome trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied

Coronary heart disease, acute coronary syndrome, impaired glucose tolerance, type 2 diabetes mellitus

Interventions
Current interventions as of 01/08/2017:
Acarbose (oral) vs placebo

The participants in the intervention group were given one tablet (50 mg) of acarbose per day to be taken with a meal during the first week (7 days). During the second week, the dose was increased to two tablets/day (50 mg twice a day; 100 mg/day), and then three tablets/day (50 mg three times a day; 150 mg/day) thereafter. The maximum tolerated dose was taken for the duration of the trial (maximum dose is 150 mg/day).

Total duration of interventions
Median duration of 3.0 years

Previous interventions:
Acarbose (oral) vs placebo.

The participants in the intervention group will be given one tablet (50 mg) of acarbose per day to be taken with a meal during the first week (7 days). During the second week, the dose is increased to two tablets/day (50 mg twice a day; 100 mg/day), and then three tablets/day (50 mg three times a day; 150 mg/day) thereafter. The maximum tolerated dose will be taken for the duration of the trial (maximum dose is 150 mg/day).

Total duration of interventions: Approximately 4 years

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Acarbose

Primary outcome measure
Current primary outcome measure as of 20/04/2018:
Major cardiovascular events (defined as: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina or hospitalisation for heart failure [MACE5]) occurring after randomisation (baseline) were identified through patient interviews at study visits, physician and/or family member reports and by searches of local or national electronic health records, death registries, or other publicly available sources (where permitted by local ethics approvals). All events were adjudicated by an independent Clinical Events Committee, blinded to therapy allocation.

Previous primary outcome measures as of 01/08/2017:
A composite cardiovascular outcome defined as the time after randomization to the first occurrence of any one of the following:
1. Cardiovascular death
2. Non-fatal MI

3. Non-fatal stroke
4. Hospitalisation for unstable angina
5. Hospitalisation for heart failure

Previous primary outcome measures:
Occurrence of any one of the following:
1. Cardiovascular death
2. Non-fatal MI
3. Non-fatal stroke

The primary and secondary outcomes will be monitored for a minimum of 4 years/participant. The outcomes will be assessed at 1, 2 and 4 months post-randomisation, and then every 4 months thereafter for the remainder of the trial.

Secondary outcome measures

Current secondary outcome measures as of 20/04/2018:
1. Individual MACE5 components and all-cause mortality were ascertained as for the primary outcome measure.
2. Transition to type 2 diabetes was ascertained from four-monthly study visit fasting plasma glucose values and by annual study visit 75g oral glucose tolerance tests, or by non-study physician reports adjudicated by an independent Clinical Events Committee, blinded to therapy allocation.
3. Transition to impaired renal function (defined as: eGFR <30 ml/min/1.73 m2, doubling of baseline serum creatinine concentration, or halving of baseline eGFR) was ascertained from annual study visit plasma creatinine measurements.
4. Medical resource use data were collected at 4-monthly study visits.

Previous secondary outcome measures as of 01/08/2017:
1. Transition to type 2 diabetes confirmed by two successive diagnostic plasma glucose values (FPG ≥7.0 mmol/l and/or 2HPG ≥11.1 mmol/l), with no intervening non-diagnostic values.
2. All-cause mortality.
3. Each of the components of the primary composite cardiovascular outcome will also be analysed individually, both as first and as total events.
4. MACE composite cardiovascular outcome, defined as the time after randomisation to the first occurrence of any one of the following:
• Cardiovascular death
• Non-fatal MI
• Non-fatal stroke
5.Proportion of patients with an impaired renal function as evidenced by:
• A reduced eGFR (<30 ml/minute/ 1.73 m2) estimated using the Chinese MDRD formula
• A doubling of the baseline plasma creatinine level
• A halving of the baseline eGRF.
6. Resource use, costs and cost effectiveness.

Previous as of 02/03/10:
1. Transition to type 2 diabetes confirmed by two successive diagnostic plasma glucose values (FPG ≥7.0 mmol/l and/or 2HPG ≥11.1 mmol/l), with no intervening non-diagnostic values
2. All cause mortality
3. Composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure or hospitalisation for unstable angina. Each of the components of this composite will also be analysed individually, both as first and as total events.
4. Proportion of patients with evidence of non-alcoholic fatty liver disease (NAFLD) as judged by

changes in ALT levels
5. Proportion of patients with an impaired renal function as evidenced by:
A reduced eGFR (<30 ml/minute/ 1.73 m2) estimated using the Chinese MDRD formula, or a doubling of the baseline plasma creatinine level, or a halving of the baseline eGRF

The primary and secondary outcomes will be monitored for a minimum of 4 years/participant. The outcomes will be assessed at 1, 2 and 4 months post-randomisation, and then every 4 months thereafter for the remainder of the trial.

Initial information at time of registration:
1. Transition to type 2 diabetes confirmed by two successive diagnostic plasma glucose values (FPG >=7.0 mmol/l and/or 2HPG >=11.1 mmol/l), with no intervening non-diagnostic values
2. All cause mortality
3. Composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure or hospitalisation for unstable angina. Each of the components of this composite will also be analysed individually, both as first and as total events.
4. Proportion of patients with evidence of non-alcoholic fatty liver disease (NAFLD) as judged by changes in alanine aminotransferase (ALT) levels
5. Proportion of patients with an impaired renal function as evidenced by a reduced eGFR (<60 ml /minute/1.73 m^2) estimated using the Chinese MDRD formula, or a doubling of the baseline plasma creatinine level

The primary and secondary outcomes will be monitored for a minimum of 4 years/participant. The outcomes will be assessed at 1, 2 and 4 months post-randomisation, and then every 4 months thereafter for the remainder of the trial.

Overall study start date
15/12/2008

Completion date
18/04/2017

Eligibility

Key inclusion criteria
Current inclusion criteria as of 31/07/2017:
1. Male or female, aged 50 years or more
2. Definite CHD, defined as a, b or c below:
a) Previous myocardial infarction (MI), or Acute Coronary Syndrome (ACS), but not within the last 3 months, with any two of the following:
i) Typical clinical presentation
ii) Confirmatory ECG changes
iii) Appropriate elevation of cardiac enzymes/biomarkers
If original reports are unavailable then alternative documentation e.g. discharge summary or a clinical note from the study Investigator describing the evidence for a previous MI will be accepted.
Note: Patients with stents are eligible.
b) Previous unstable angina (UA) or Acute Coronary Syndrome (ACS), but not within the last 3 months, with any two of the following:
i) Typical clinical presentation
ii) Confirmatory ECG changes

iii) Either elevation of a cardiac biomarker or a >50% stenosis in ≥1 major epicardial coronary artery shown on coronary angiography or CT angiography. Where stenosis is reported in a qualitative manner, the categories “moderate” and “severe” will be taken as equating to >50% stenosis.
c) Current stable angina defined as:
i) Typical clinical history with symptoms occurring within the last month, and
ii) A >50% stenosis in ≥1 major epicardial coronary artery shown on coronary angiography or CT angiography. Where stenosis is reported in a qualitative manner, the categories “moderate” and “severe” will be taken as equating to >50% stenosis.
3. Impaired glucose tolerance diagnosed on a single standard OGTT, defined as a 2- hour plasma glucose (2HPG) value ≥7.8 but <11.1 mmol/l and a fasting plasma glucose(FPG) <7.0 mmol/l within six months prior to enrollment.
4. Optimised cardiovascular drug therapy.
5. At least 80% adherent to single blind placebo Study Medication during the run-in period.
6. Provision of written informed consent.

Correct inclusion criteria as of 14/06/2017:
1. Male or female, aged 50 years or more
2. Definite CHD, defined as a, b or c below:
2.1 Previous myocardial infarction (MI) or Acute Coronary Syndrome (ACS), but not within the last 3 months, with any two of the following:
2.1.1. Typical clinical presentation
2.1.2. Confirmatory ECG changes
2.1.3. Appropriate elevation of cardiac enzymes/biomarkers
Note: Patients with stents are eligible.
2.2 Previous unstable angina (UA) or Acute Coronary Syndrome (ACS), but not within the last 3 months, with any two of the following:
2.2.1. Typical clinical presentation
2.2.2.Confirmatory ECG changes
2.2.3.Either elevation of a cardiac biomarker or a >50% stenosis in ≥1 major epicardial coronary artery shown on coronary angiography or CT angiography. Where stenosis is reported in a qualitative manner, the categories moderate and severe will be taken as equating to >50% stenosis.
2.3. Current stable angina defined as:
2.3.1. Typical clinical history with symptoms occurring within the last month, and
2.3.2. A >50% stenosis in ≥1 major epicardial coronary artery shown on coronary angiography or CT angiography. Where stenosis is reported in a qualitative manner, the categories moderate and severe will be taken as equating to >50% stenosis.
3. Impaired glucose tolerance diagnosed on a single standard OGTT, defined as a 2-hour plasma glucose (2HPG) value ≥7.8 but <11.1 mmol/l and a fasting plasma glucose(FPG) <7.0 mmol/l within six months prior to enrollment.
4. Optimised cardiovascular drug therapy
5. At least 80% adherent to single blind placebo Study Medication during the run-in period
6. Provision of written informed consent

Previous inclusion criteria as of 02/03/10:

2.1. Previous myocardial infarction (MI), but not within the last 3 months, with at least two of the following:
2.2 Previous unstable angina, but not within the last 3 months, with all of the following:
2.2.1. Typical clinical presentation
2.2.2. Dynamic ECG changes

2.2.3. Either elevation of a cardiac biomarker or a >50% stenosis in ≥1 major epicardial coronary artery shown on coronary angiography
2.3. Current stable angina defined as:
2.3.1. Typical clinical history with symptoms occurring within the last month, and
2.3.2. A >50% stenosis in ≥1 major epicardial coronary artery shown on coronary angiography
3. Impaired glucose tolerance diagnosed on a single 75g anhydrous glucose OGTT, defined as a 2-hour plasma glucose (2HPG) value ≥7.8 but <11.1 mmol/l and a fasting plasma glucose (FPG) <7.0 mmol/l

Previous inclusion criteria at time of registration:
1. Male or female, aged 50 years or more
2. Definite CHD, defined as a, b or c below:
2.1. Previous myocardial infarction (MI), but not within the last 3 months, with all of the following:
2.1.1. Typical clinical presentation
2.1.2. Confirmatory electrocardiogram (ECG) changes
2.1.3. Appropriate elevation of cardiac enzymes/biomarkers
2.2. Previous unstable angina, but not within the last 3 months, with all of the following:
2.2.1. Typical clinical presentation
2.2.2. Dynamic ECG changes
2.2.3. Either elevation of a cardiac biomarker or a >50% stenosis in >=1 major epicardial coronary artery shown on coronary angiography
2.3. Current stable angina with both of the following:
2.3.1. Current and typical clinical history
2.3.2. A >50% stenosis in >=1 major epicardial coronary artery shown on coronary angiography
3. Impaired glucose tolerance diagnosed on a single 75 g anhydrous glucose OGTT, defined as a 2-hour plasma glucose (2HPG) value >=7.8 but <=11.1 mmol/l and a fasting plasma glucose (FPG) <7.0 mmol/l
4. Optimised cardiovascular drug therapy
5. At least 80% adherent to single-blind placebo Study Medication during the run-in period
6. Provision of written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
50 Years

Sex
Both

Target number of participants
6500

Total final enrolment
6522

Key exclusion criteria

Current information as of 01/08/2017:
1. Previous history of diabetes, other than gestational diabetes.
2. MI, unstable angina, stroke or a transient ischaemic attack (TIA) within the previous three months.
3. Planned or anticipated coronary, cerebrovascular or peripheral arterial revascularisation or other major surgical intervention, at the time of randomisation.
4. NYHA class III or IV heart failure.
5. Evidence of severe hepatic disease.
6. Evidence of severe renal impairment or an eGFR <30 ml/min/1.73m2 (derived using the MDRD Chinese equation).
7. Any other condition likely to reduce adherence to the protocol e.g. alcoholism, major active psychiatric disorder, cognitive impairment or a condition likely to markedly limit life expectancy e.g. malignancy.
8. Pregnancy (or planned pregnancy within the next five years).
9. Concurrent participation in any other clinical interventional trial. Note: Patients who were treated previously with an alphaglucosidase inhibitor must have at least a three-month washout period before being randomised into the ACE trial.
10. Known intolerance to alpha glucosidase inhibitors or gastrointestinal problems.
11. Thought by the investigator for any reason to be unsuitable for participation in this clinical study.

previous exclusion criteria as of 02/03/10:
1. Previous history of diabetes, other than gestational diabetes.
2. MI, unstable angina, stroke or a transient ischaemic attack (TIA) within the previous three months.
3. Planned or anticipated coronary, cerebrovascular or peripheral arterial revascularisation or other major surgical intervention.
4. New York Heart Association (NYHA) class III or IV heart failure.
5. Evidence of severe hepatic disease.
6. Evidence of severe renal impairment or an eGFR <30 ml/min/1.73m2 (derived using the MDRD Chinese equation)
7. Any other condition likely to reduce adherence to the protocol e.g. alcoholism, major active psychiatric disorder, cognitive impairment or a condition likely to markedly limit life expectancy e.g. malignancy.
8. Pregnancy (or planned pregnancy within the next five years).
9. Concurrent participation in any other clinical interventional trial. Added 14/06/2017: Note: Patients who were treated previously with an alphaglucosidase inhibitor must have at least a three-month washout period before being randomised into the ACE trial.
10. Known intolerance to alpha glucosidase inhibitors or gastrointestinal problems.
11. Thought by the investigator for any reason to be unsuitable for participation in this clinical study.

Initial information at time of registration:
1. Previous history of diabetes, other than gestational diabetes
2. MI, stroke or a transient ischaemic attack (TIA) within the previous three months
3. Planned or anticipated coronary, cerebrovascular or peripheral arterial revascularisation or other major surgical intervention
4. New York Heart Association (NYHA) class III or IV heart failure
5. Evidence of severe hepatic disease
6. Evidence of severe renal impairment or an estimated glomerular filtration rate (eGFR) <30 ml

/min/1.73 m^2 (derived using the MDRD Chinese equation)
7. Any other condition likely to reduce adherence to the protocol e.g., alcoholism, major active psychiatric disorder, cognitive impairment or a condition likely to markedly limit life expectancy e.g., malignancy
8. Pregnancy (or planned pregnancy within the next five years)
9. Concurrent participation in any other clinical interventional trial
10. Known intolerance to alpha glucosidase inhibitors or gastrointestinal problems
11. Thought by the investigator for any reason to be unsuitable for participation in this clinical study

Date of first enrolment
17/02/2009

Date of final enrolment
10/09/2015

Locations

Countries of recruitment
China

England

United Kingdom

Study participating centre
Diabetes Trials Unit
Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM)
Churchill Hospital
Old Road
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United Kingdom
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Study participating centre
176 hospitals in China
China
-

Sponsor information

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Sponsor type
University/education

Website
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ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Industry

Funder Name
Bayer

Results and Publications

Publication and dissemination plan
The primary results were presented at the European Association of the Study of Diabetes in Lisbon on 13 September 2017 and published online the same day in the Lancet Diabetes Endocrinology journal, and in print in November 2017 http://www.thelancet.com/journals/landia/article/PIIS2213-8587(17)30309-1/fulltext.
Further results were presented at the International Diabetes Federation World Diabetes Congress in Abu Dhabi on the 6 December 2017.
A number of secondary manuscripts are in preparation.

Intention to publish date
13/09/2017

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/11/2017		Yes	No
Other publications	Medical resources and costs	01/11/2023	02/11/2023	Yes	No