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Metformin against gliclazide in patients with diabetes and heart failure

Submission date 29/04/2010	**Recruitment status** Stopped	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 29/04/2010	**Overall study status** Stopped	
Last Edited 24/04/2019	**Condition category** Circulatory System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2006-002812-87

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
4836

Study information

Scientific Title
Metformin against gliclazide in patients with diabetes and heart failure: a randomised open label study

Acronym
MAGPDF

Study objectives
Hypothesis:
In patients with symptomatic left ventricular systolic dysfunction and type 2 diabetes, biguanide therapy compared to a sulphonylurea urea (Gliclazide), will improve ventricular function and vascular endothelial function.

Summary:
There are a large number of patients with both diabetes and heart failure in the UK because diabetes causes heart failure and likewise heart failure causes diabetes. Metformin and Gliclazide are two commonly prescribed diabetic medications in these patients but there is no information on which is better for the patient. In this study we will look at the effects of these two medications on the function of the heart muscle, blood vessels and symptoms in patients with diabetes and heart failure.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Hull and East Riding Research Ethics Committee (now superseded by Leeds (West) REC), 18/07/2006, ref: 06/Q1104/98

Study design
Randomised interventional treatment 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 below to request a patient information sheet

Health condition(s) or problem(s) studied
Topic: Cardiovascular; Subtopic: Cardiovascular (all Subtopics); Disease: Cardiovascular

Interventions

Follow-up:
Patients will be reviewed each month for symptom assessment using the standardised symptom questionnaire and EQ5-D. Patients will also undergo physical examination including body weight and fat composition by impedance measurement. Blood tests (non-fasting) for serum HbA1c, U&E's and blood glucose levels. Doses of the study drug (Gliclazide or Metformin) will be increased to maximum (metformin 1 g three times a day [tds] or gliclazide 160 mg twice daily [bd]) if there is inadequate diabetic control as evidenced by blood sugar readings and HbA1c levels. If this is inadequate to maintain glucose control, then agents other than a biguanide or sulphonylurea can be added to this regimen.

At 8 months all baseline tests, as described above, will be repeated and in addition the patients will undergo dobutamine stress and recovery cardia magnetic resonance (CMR) and forearm blood flow quantification as described below. We intend to conduct dobutamine stress and recovery CMR and forearm blood flow measurements only once at 8 months (final follow-up). We could, if requested, also do these tests at baseline but this would add an extra burden to patients and extra costs but make little further contribution to addressing the primary hypothesis of differences between treatments. The study is randomised and so the two populations should be similar, which can be assessed by comparing other baseline values.

CMR Methodology:
Cardiac magnetic resonance (CMR) imaging will be performed in a 1.5T Clinical Scanner (General Electric). Heart rate and blood pressure would be monitored throughout the imaging protocol.

Cine-CMR:
Left ventricular function and volumes will be quantified at rest and after Dobutamine stress with a breath hold gated gradient echo sequence (cine-MR). Incremental doses of dobutamine, 5 - 40 mg/kg/min, will be infused intravenously. Dobutamine infusion will be continued until patients develop symptoms of myocardial ischaemia, significant arrhythmias, or achieve target heart rate. Intravenous atropine will be used if necessary to increase heart rate. Cine-MR images will be acquired at rest and at five-minute intervals for 45 minutes during recovery following Dobutamine stress.

Gadolinium contrast CMR:
First pass gadolinium enhanced imaging with a saturation recovery turboflash sequence will be done for assessment of myocardial perfusion and delayed hyperenhancement (DE-CMR) with a segmented inversion-recovery fast gradient echo sequence for assessing myocardial viability. Studies will be conducted at the same time of day, approximately 4 hours after the last intake of medication and with a similar diet in the 3 days prior to scanning as assessed by a dietary diary.

All CMR images will be sent to a Linux-based off-line workstation for analysis. The scans will be placed in random order after the identity markers have been removed. The cine and gadolinium-enhanced CMR images will be evaluated separately by the consensus of two experienced observers.

Cine images will be used to calculate LV end-diastolic volume, end-systolic volume, ejection fraction, and myocardial mass at end-diastole with the use of analytical MRI-MASS software. Epicardial and endocardial borders of the left ventricle excluding papillary muscles and trabeculations will be traced semi-automatically in contiguous short axis slices. End-systolic volumes will be adjusted for ventricular long-axis shortening, which will be accomplished by eliminating from calculation the basal slices encompassing the left atrium at end systole.

Forearm blood flow measurement:
Contrast enhanced ultrasound (CEU) imaging of the forearm muscles in short-axis will be performed with intermittent ultraharmonic imaging (Sonos 5500, Philips Ultrasound) at a transmission frequency 1.3 MHz, and a mechanical index of 1.0. For CEU lipid-shelled decafluorobutane microbubbles (DMP 115, Bistol Myers Squibb) suspended in saline (4 x 10^6 ml) will be infused intravenously at 1.5 to 2.5 ml/min. CEU images will be acquired at rest (CEU-R) and after an intravenous infusion of insulin (CEU-I) for 60 minutes (1 mU/kg/min and 5 mU/kg /min). Euglycaemia will be maintained with a variable rate of 20% dextrose infusion intravenously. Heart rate, blood pressure, and blood glucose levels will be monitored every 5 to 10 minutes throughout the protocol.

Digitally acquired CEU will be analysed off-line with custom written software to quantify skeletal muscle blood volume and red blood cell velocity as described previously. Skeletal muscle blood flow reserve is then given by the ratio of blood flow measured during infusion of insulin and at rest.

Total brachial artery blood flow will be quantified by 2-D and Doppler ultrasound with a 7 MHz linear-array transducer (Sonos 5500, Philips). Brachial artery blood flow will be measured by the product of vessel cross sectional area, calculated from videocaliper measurement of the diameter and the centerline time-averaged peak velocity (cm2) determined from arterial pulsed-wave Doppler, with an angle correction of 60°.
Study entry: single randomisation only

Intervention Type
Other

Phase
Phase IV

Primary outcome measure
Difference in left ventricular end-systolic volume between patients randomised to metformin compared to gliclazide at 8 months

Secondary outcome measures
Differences between the two groups in serum NT-pro BNP levels in:
1. Time to recovery of LV function after dobutamine stress
2. Insulin mediated flow reserve quantified by contrast enhanced ultrasound and markers of endothelial function
3. Average symptom score of all monthly follow-ups, which avoids undue emphasis being placed on a single time-point (patients who are withdrawn for worsening heart failure or who die will be assigned worst rank for symptom assessment at all subsequent time-points)

Overall study start date
24/10/2006

Completion date
01/09/2010

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Diabetes on oral hypoglycaemic agents (OHGA)
2. Heart failure
3. Male and female, lower age limit of 18 years

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 60

Key exclusion criteria
1. Diabetes on insulin
2. No left ventricular function (LVF)

Date of first enrolment
24/10/2006

Date of final enrolment
01/09/2010

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Department of Cardiology
Cottingham
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Sponsor information

Organisation
Hull and East Yorkshire Hospitals NHS Trust (UK)

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Sponsor type
Hospital/treatment centre

Website
http://www.hey.nhs.uk/HomeContentWithNews.aspx?PageID=1&SectionID=1

ROR
https://ror.org/01b11x021

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (BHF) (UK)

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration