REducing with MetfOrmin Vascular Adverse Lesions in Type 1 diabetes mellitus

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Primary objective: To test for the first time in a double-blind randomized, placebo controlled trial whether three years treatment with metformin 1000 mg bd added to titrated insulin therapy (towards target HbA1c 7.0%/ 53 mmol/mol) reduces...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON43685

Source
ToetsingOnline

Brief title
REMOVAL

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
juvenile diabetes, Type 1 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W,Juvenile Diabetes Research Foundation (UK),Merck

Intervention

Keyword: Diabetes mellitus type 1 Cardiovascular complication, Intima media thickness, Metformin

Outcome measures

Primary outcome

progression of averaged mean far wall common carotid artery IMT (CCA cIMT,

measured in mm, at baseline, 12, 24 and 36 months).

Secondary outcome

Secondary endpoints:

(i) HbA1c;

(ii) LDL cholesterol;

(iii) albuminuria & estimated glomerular filtration rate

(iv) retinopathy stage (ETDRS stage = Early Treatment Diabetic Retinopathy

Study);

(v) weight

(vi) insulin dose;

(vii) endothelial function (in some centres).

N.B. We will consider a statistically significant improvement in two or more of

these secondary endpoints to be a clinically meaningful result with the

potential to influence clinical practice.

Tertiary endpoints: To compare between treatment groups, as above, change in:

(i) frequency of hypoglycaemia;

(ii) treatment satisfaction;

(iii) markers of endothelial function (t-PA, sE-selectin, sICAM-1);

(iv) progression of averaged maximal distal common carotid artery IMT (CCA cIMT,

measured in mm, at baseline, 12, 24 and 36 months).

(v) vitamin B12 status

Study description

Background summary

Cardiovascular disease (CVD) is the commonest cause of premature death in type 1 diabetes (T1DM). Population-based data from 19,248 individuals with the condition in Scotland indicate ten year absolute CVD event rates of 16.7% and 12.7% respectively in men and women aged 40-60 years, rising to 49% and 39% in those aged over 60 years. These rates are 3-5 fold higher than in the general population. Few randomized controlled trials (RCTs) have directly addressed myocardial infarction (MI) and stroke prevention in T1DM.
Metformin has many of the properties desirable for an adjunct oral agent to be added in with insulin therapy to improve metabolic control. Data from ourselves and others show that it may: (i) reduce insulin dose (by 6 units) for a given achieved HbA1c; (ii) promote weight stabilization; (iii) be associated with low rates of hypoglycaemia; and (iv) reduce LDL cholesterol * by 0.5 mmol/L (20 mg/dL) - even on a background of statin
therapy. There is considerable evidence that it may also provide direct and potentially beneficial cardiovascular effects at least in type 2 diabetes - particularly as demonstrated in the UK Prospective Diabetes Study (UKPDS).

Study objective

Primary objective:
To test for the first time in a double-blind randomized, placebo controlled trial whether three years treatment with metformin 1000 mg bd added to titrated insulin therapy (towards target HbA1c 7.0%/ 53 mmol/mol) reduces atherosclerosis, as measured by progression of carotid Intima Media Thickness (IMT), in adults with confirmed T1DM aged 40 years and over at increased risk for CVD.
Secondary and tertiary objective:
To examine over this period the effect of metformin on other markers of diabetic micro- and macrovascular complications and intermediate disease- related biomarkers. The composite secondary endpoint will provide clinically meaningful information on the potential of metformin to influence clinical practice in this condition.

Study design

Randomized, double-blind, placebo controlled trial

Intervention

Metformin as Glucophage 500mg two tablets twice daily (=1000mg twice daily) or matching placebo tablets, added to standard insulin therapy. Participants will be asked to titrate up the medication according to usual practice with metformin i.e. they will take one tablet with the evening meal for one week; this will then be increased to additional tablets at weekly intervals with the morning meal, evening meal and then morning meal until a dose of 1000 mg twice daily is achieved.

Study burden and risks

Patients will have to visit the research ward 5 times over a period of three years. The remaining visits will be planned together with their standard outpatient visits. Furthermore, patients will be called regelurly, in particular at initiation of the study, to monitor their glucose-regulation. Additional blood will be withdrawn (approximately 60 ml in total spread over 5 withdrawals). Potential risks are hematoma, which is reversible. Treatment of metformin can lead to hypoglycemia when added to standard insulin therapy. These episodes will be kept to a mininum by excluding those patients with a hypoglycemia anawareness and to monitor patients frequently when therapy is initiated. Rare complications of metformin therapy are elevated liver enzymes and lactic acidosis. The former is reversible and will be discovered at an early stage, since these levels will be monitored frequently after initiation of therapy. Lactic acidosis is associated with impaired kidney function. Patients with kidney function will be excluded from the study. Furthermore, patients will be instructed to contact the study doctor when there is a risk of deterioration of kidney function, i.e. when contrast is given for diagnostic testing and when a new drug is started.
Potential benefits: patients will more closely than conventional followed with regard to glucose regulation and cardiovascular risk.

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

Type 1 diabetes for five years or more*; age * 40 years; 7.0 * HbA1c < 10.0% (53-86 mmol/mol) ;AND three or more of the following ten CVD risk factors:
(i) BMI * 27 kg/m2
(ii) current HbA1c > 8.0% (64 mmol/mol)
(iii) known CVD/ peripheral vascular disease
(iv) current smoker
(v) eGFR < 90 ml/ min/ 1.73 m2
(vi) micro- (or macro-) albuminuria [according to local assays and reference ranges]
(vii) hypertension (BP¬*140/ 90 mmHg; or established on antihypertensive treatment)
(viii) dyslipidaemia [total cholesterol*5.0 mmol/L (200 mg/dL); or HDL cholesterol<1.20 mmol/L (46 mg/dL) [men] HDL cholesterol<1.30 mmol/L (50 mg/dL) [women]; or fasting triglycerides*1.7 mmol/L (150 mg/dL); or established on lipid-lowering treatment
(ix) strong family history of CVD (at least one parent, sibling or aunt/uncle with myocardial infarction, CABG or stroke aged < 60 years)
(x) duration of diabetes > 20 years.;* Type 1 diabetes is defined as diagnosis below age 40 years AND insulin use within 1 year of diagnosis

Exclusion criteria

(i) Women of childbearing age (i.e. continuing menstrual cycle) not using effective contraception
(ii) Pregnancy and/or lactation; planning to get pregnant or not using effective contraception
(iii) Patients with Acute Coronary Syndrome or Stroke/ Transient Ischaemic Attack within the

last three months
(iv) Symptomatic angina on mild or moderate exertion
(v) Stage 3 or 4 heart failure defined according to the NYHA criteria
(vi) Estimated glomerular filtration rate < 45 ml/min/1.73m2 (MDRD)
(vii) Contraindications to metformin
- hepatic impairment (ALT > 3.0 times ULN)
- known hypersensitivity to metformin
- acute illness [dehydration, severe infection, shock, acute cardiac failure]
- suspected tissue hypoxia
(viii) Metformin treatment for more than three months within last two years
(ix) Anaemia (haemoglobin < 10.0 g/dL)
(x) Ongoing treatment with oral steroids, pramlintide or GLP-1 agonist therapy
(xi) Hypoglycaemia unawareness confirmed as significant by site Principal Investigator
(xii) Impaired cognitive function/ unable to give informed consent
(xiii) Previous carotid surgery or inability to capture adequate carotid images
(xiv) Gastroparesis (on gastric emptying studies) confirmed as significant by site Principal Investigator OR more than two hospital admissions with unexplained vomiting in last year
(xv) history of biochemically-confirmed acidosis (with lactate > 5.0 mmol/L)
(xvi) Any coexistent life-threatening condition including diagnosis of cancer within prior two years
(xvii) history of alcohol problem or drug abuse
(xviii) diabetes other than type 1 diabetes (e.g. secondary to pancreatitis, pancreatectomy or primary pancreatic disease)
(xix) Involvement in a clinical trial involving an investigational medicinal product within the last six months

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):	24-08-2012
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Glucophage
Generic name:	Metformin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-01-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-04-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-01-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-12-2013
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-01-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2011-000300-18-NL
ClinicalTrials.gov	NCT01483560
CCMO	NL37333.068.11