Metformin for AAA Growth Inhibition: A randomized controlled trial

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This study has been transitioned to CTIS with ID 2024-517387-37-00 check the CTIS register for the current data. The proposed multi-center population-based open-label randomized controlled trial with blinded outcome assessment will examine if...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Aneurysms and artery dissections
Study type	Interventional

Summary

ID

NL-OMON51630

Source
ToetsingOnline

Brief title
MAAAGI trial

Condition

- Aneurysms and artery dissections

Synonym
aortic Aneurysm, aortic dilatation

Research involving
Human

Sponsors and support

Primary sponsor: Uppsala University
Source(s) of monetary or material Support: instelling zelf

Intervention

Keyword: Abdominal, Aortic Aneurysm, Cardiovascular Diseases, Metformin, Physiological Effects of Drugs

Outcome measures

Primary outcome

To examine if up to 2g metformin administered daily over a five-year period reduces AAA growth as measured by computed tomography (CT) imaging of AAA diameter in patients with small AAAs who do not have diabetes. An interim STOP/GO analysis will be performed after two-years of treatment.

Secondary outcome

Secondary objectives

To examine if metformin limits increase in; a) CT-assessed AAA volume; b) ultrasound assessed AAA diameter; c) improves health-related quality of life; d) reduces the need for surgery (diameter >=55mm) or rupture; and e) represents a cost-effective treatment to reduce the need for AAA surgery.

Exploratory objectives

To examine; a) if there is a dose or time related response of metformin regarding the primary or secondary endpoints; and b) if metformin favorably modifies circulating inflammation and matrix remodeling biomarkers; or c) affects perivascular adipose tissue.

Safety objective

To determine adverse events; primarily related to known side effects of

metformin and possible unexpected effects on AAA, related to metformin

treatment after two and five years.

Study description

Background summary

Abdominal aortic aneurysm (AAA) is a major health issue and ruptured AAA a common cause of death in Europe and North America. Worldwide 200.000 annual deaths are attributed to AAA. To prevent rupture, early detection and preventive surgical repair in selected individuals is recommended. AAA screening programs are already implemented in the UK, Sweden and the USA. Most screening detected AAAs are, however, small (diameter 30-54 mm) and are under surveillance until expansion to the threshold for elective surgical repair; i.e. diameter >=55 mm for men and >=50 mm for women. 70% of the men and women who are being monitored for small AAAs, eventually will require surgical repair. In 2015, ~1200 AAA repairs were performed in Sweden at a cost of ~30 million Euros. In the Netherlands even more AAA repairs are performed, 3300 a year. AAA repair is associated with significant mortality (1-5%), perioperative complications (up to 20%), cost (~25,000 Euros/patient) and need for life-long post-operative follow-up, imaging and repeat surgery (in~20% of cases).

A key limitation of contemporary treatment strategies of AAA is the lack of therapy directed at small AAA. Although surgical repair is an effective treatment for large AAA, several large trials have shown that early surgery of small AAA does not reduce mortality. Given that AAA diameter is the strongest predictor for rupture and the natural course for AAA is continued expansion, a mean to reduce AAA growth rate would be highly beneficial. Commonly used cardiovascular drugs, such as anti-platelet drugs, statins, angiotensin converting enzyme inhibitors and beta-blockers have not been shown to slow AAA growth in cohort studies. Previous interventional trials with therapy directed at AAA growth reduction include antibiotics, mast cell inhibitors, beta-blockers, platelet inhibitors, and angiotensin converting enzyme blockers, with trials of stem cells and cyclosporine under way. These trials have all been either small, with negative results or had unacceptable side effects.

Risk factors for AAA often mimic those of arteriosclerosis, with the notable exception of diabetes mellitus. Several large trials have shown that people with diabetes are less likely to develop AAA and when they do; the AAA expands slower and is less likely to rupture. However, in 2016 a study of 58 patients with diabetes reported that the drug metformin, the world*s most widely used drug for type II diabetes, was associated with reduced AAA growth. Following this, a cohort study of 1.2 million patients with diabetes, reported that

metformin prescription was associated with a 36% reduced risk of developing an AAA and in a cohort of 1755 AAA patients a 36-76% slower AAA growth rate were reported in patients with diabetes and metformin prescription, but not those without. A similar finding was made in a cohort of 13,834 American veterans with AAA and diabetes where metformin was independently associated with reduced growth rates of AAA of different sizes.

Metformin may reduce AAA growth by inhibiting key pathological mechanisms implicated in AAA, including inflammation and extracellular matrix remodeling. Two different rodent models of AAA have found that metformin may reduce AAA growth in euglycemic animals. These studies suggest that metformin may reduce AAA growth by reducing aortic inflammation, elastin degradation, smooth muscle cell depletion and monocyte infiltration independent of glucose levels.

In Sweden, data from a cohort of 526 patents under surveillance for small AAA support these findings with a reduced AAA growth rate and altered cytokine expression in patients prescribed metformin. In a connected experimental animal study, metformin was also shown to inhibit AAA formation, improve endothelial vasomotor function and reduce pro- inflammatory gene expression in euglycemic mice.

Metformin is a well-established first-line treatment of type II diabetes. It acts primarily by reducing blood glucose levels by inhibiting hepatic glucose production and increase insulin sensitivity. It is cheap, safe and able to reduce micro- and macrovascular complications and overall death (UKPDS 1998, Holman 2008, Griffin 2017). This has prompted several large trials of metformin given to persons without diabetes showing that metformin is safe and highly tolerable in variable patient groups.

Metformin is available as a generic drug at low cost. It is generally well tolerated, with few serious side effects. Gastrointestinal problems may occur primarily in the run-in phase. This is usually mitigated by taking metformin with a meal and increasing the dose stepwise over a course of several weeks to the desired level.

As metformin is a generic drug there is no commercial interest in exploring its potential as a drug to reduce AAA growth, necessitating an academically driven trial. The rationale for this randomized controlled trial is to investigate whether treatment with Metformin inhibits growth of small AAAs.

Study objective

This study has been transitioned to CTIS with ID 2024-517387-37-00 check the CTIS register for the current data.

The proposed multi-center population-based open-label randomized controlled trial with blinded outcome assessment will examine if metformin slows AAA

growth in patients with small AAAs who do not have diabetes.

Primary objective
To examine if up to 2g metformin administered daily over a five-year period reduces AAA growth as measured by computed tomography (CT) imaging of AAA diameter in patients with small AAAs who do not have diabetes. An interim STOP/GO analysis will be performed after two-years of treatment.

Secondary objectives
To examine if metformin limits increase in; a) CT-assessed AAA volume; b) ultrasound assessed AAA diameter; c) improves health-related quality of life; d) reduces the need for surgery (diameter >=55mm) or rupture; and e) represents a cost-effective treatment to reduce the need for AAA surgery.

Exploratory objectives
To examine; a) if there is a dose or time related response of metformin regarding the primary or secondary endpoints; and b) if metformin favorably modifies circulating inflammation and matrix remodeling biomarkers; or c) affects perivascular adipose tissue.

Safety objective
To determine adverse events; primarily related to known side effects of metformin and possible unexpected effects on AAA, related to metformin treatment after two and five years.

Study design

The MAAAGI-trial is a population-based multi-center, prospective, parallel group, randomized, open label trial with blinded outcome assessment to assess if metformin up to 2g daily over a five-year period will reduce AAA growth in patients who do not have diabetes.

Patients will be recruited from a cohort of patients with diagnosed AAA at one Dutch side e.g., Amsterdam UMC, Amsterdam and seven Swedish sides.
The patients should have a maximum aortic diameter of 30-49 mm for men and 30-44 mm for women, who do not have diabetes and be expected to tolerate metformin. A total of 500 patients with AAA will be included in the study, 250 in each study arm. Patients will be randomized to metformin or standard care in a 1:1 ratio. At the Amsterdam UMC, 100 patients will be randomized in a 1:1 ratio to each arm.

The patients are scheduled for one enrolment visit, eight study visits and ten phone contacts for those randomized to metformin (three to support titration of study drug) and seven phone contacts for those randomized to standard care. The study visits will take place at the vascular laboratory at the respective surgical departments for clinical examination and blood sampling and at the CT units at the radiology departments where CT-imaging will be performed. The

study visits and 7 telephone conversations are also part of standard care.

After a run in phase to support titration of metformin, visits and phone contacts are scheduled to alternate every three months until 24 months and twice yearly thereafter. CT imaging and AAA US will be performed at baseline, 24 months and end of study, as well as if necessary according to clinical routine. Study drug will start at baseline and continue through completion.

End of study is defined as 1) study completion at 60 months, or 2) discontinuation from study before that for any reason, for example due to AAA repair or patients will.

When all patients have completed the 24-month follow-up (including imaging) an interim analysis will be performed to assess for efficacy and safety; if there is no trend towards a positive effect or signs of a harmful effect of metformin, the study will be stopped at this phase. If there is a significant beneficial or harmful effect of metformin, the study will also be stopped at this phase.

Intervention

The treatment allocation in this study will consist of:

Study Arm 1: Metformin tablets taken orally with target dose of 2g daily

Study Arm 2: Standard care as described in current AAA guidelines (Wanhainen 2019)

Standard care includes help with smoking cessation if applicable; encouragement of physical activity and a healthy diet; blood pressure control; statin and anti-platelet therapy treatment if the patient have clinical manifestations of atherosclerotic disease. Local guidelines dictate which classes of drugs are recommended and who is responsible for treatment and follow up. The study participants allocated to metformin receive standard care plus metformin treatment.

Patients will be encouraged to take metformin every day at similar times, preferably with a meal to minimize side effects. Metformin is titrated stepwise to avoid gastrointestinal side effects. Starting dose is one tablet of metformin 500 mg day 1-14, two tablets day 15-28, three tablets day 29-42 and four tablets daily from day 43 till the remainder of the study. If a patient misses one dose he/she is encouraged to take one extra tablet with the following dose. No more than one dose should be compensated for if missed.

If a patient has severe side effects in the run-in phase, titration to target dose will be slowed. If a patient has severe side effects at the target dose, the target dose will be reduced to a level at which the side effects are

tolerable and stay at this level for the remainder of the study. Target dose and compliance to this dose is recorded at each contact.

Target dose of metformin 2 gr is chosen to reflect doses given in observational studies. It is predicted to be a sufficient dose to translate to a meaningful biologic effect whilst still safe and with acceptable side effects. The option to reduce the dose is expected to reduce drop-out rate. Once the final target dose is reached a different metformin tablet strength may be used for convenience i.e., 1 gr rather than 500 mg tablets.

Study burden and risks

The uncertain knowledge state supporting the study-hypothesis emphasizes the importance of a risk assessment for each patient. A risk determination of potential risks in this study has

Risks:
1. Suspected drug related adverse event, such as gastrointestinal events
2. Patient require surgery or intravenous contrast media during study
3. Patient develops suspect or manifest dehydration during study
4. Patient develops suspect or manifest hypoxia during study
5. Patient requiring continuous treatment with drugs that may temporarily affect renal function, such as NSAIDs
6. Patient develops B12 deficiency secondary to metformin treatment

Actions:
1. If not tolerated, treatment with study drug should be reduced in dose or stopped, temporarily or permanent, and appropriate medical action should be initiated according to the nature and severity of the AE.
2. Temporary discontinuation of the study drug according to clinical praxis for metformin. Typically 48 h after intravenous contrast media, in the perioperative phase and during fasting.
3. If risk of dehydration for any reason the study drug is temporarily discontinued. This typically includes but is not limited to fever, serious infection, vomiting, diarrhoea and reduced fluid intake.
4. If risk of hypoxia for any reason the study drug is temporarily discontinued. This typically includes but is not limited to, sepsis, chock, myocardial infarction and decompensated heart failure.
5. Study drug should be discontinued during treatment if there is evidence of renal impairment
6. S-B12 levels are controlled every 24 months and replacement therapy is initiated if indicated

Benefits:
- Other than obtaining an extensive medical evaluation and close monitoring of the AAA, no clear benefit was identified for the patients who participate in

the study.

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

Provision of written informed consent.
Male and female patients.
Age 50-80 years.
Documented AAA Ø 30-49 mm for men and 30-44 mm for women.
Fasting p-glucose <7.0 mmol/L (WHO 1999). Fasting is defined as no caloric intake for >=8 h.

Exclusion criteria

1. Short expected survival.
2. History of current or previous diabetes mellitus.
3. Current or previous use of metformin.
4. Not expected to tolerate metformin.
5. Contraindications to metformin treatment according to SmPC:
- Renal failure with glomerular filtration rate (GFR) <45ml/min according to the revised Lund-Malmo* formula.
- Hypersensitivity to metformin or any of the excipients included in the tablet.
- Acute metabolic acidosis.
- Diabetic pre-coma.
- Acute conditions with the potential to alter renal function such as; dehydration, severe infection or shock.
- Acute or chronic disease which may cause tissue hypoxia such as; decompensated heart failure, respiratory failure, recent myocardial infarction or shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
6. Known or suspected connective tissue disorder (Marfans syndrome, etc), infected or inflammatory aneurysm, aneurysm development after aortic dissection or previous surgery of the infrarenal aorta.
7. Enrolment in either another investigational drug or medical device study or another investigational study of an approved drug or medical device within 30 days prior to enrolment of the current study.
8. If, in the opinion of the investigator, it is not in the patient*s medical interest to participate in the study or the patient is unlikely to be able to comply with the study protocol.
9. Pregnancy. Women of childbearing potential are only included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test as well as willingness to comply with highly effective anti-contraception throughout the study period.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2022
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Metformin
Generic name:	Glucophage, Riomet, Fortamet, Glumetza, Obimet, Dianben, Diabex, Diaformin, Metformax
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	10-08-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-517387-37-00
EudraCT	EUCTR2018-004289-33-NL
ClinicalTrials.gov	NCT04224051
CCMO	NL80569.029.22