EffecTs of Amlodipine and other Blood PREssure Lowering Agents on Microvascular FuncTion in Small Vessel Diseases

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Primary objective:To test the hypothesis that the calcium channel blocker amlodipine has a superior beneficial effect on cerebrovascular reactivity in patients with symptomatic SVDs when compared to either the Angiotensin II type 1 (AT1) receptor...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON53102

Source
ToetsingOnline

Brief title
TREAT-SVDs

Condition

- Central nervous system vascular disorders
- Vascular hypertensive disorders

Synonym
Cerebral small vessel disease, stroke and dementia

Research involving
Human

Sponsors and support

Primary sponsor: Klinikum der Universität München (KUM)
Source(s) of monetary or material Support: Europesie unie;2020HORIZON research grant

Intervention

Keyword: cerebrovascular reactivity, Hypertension, Small vessel disease, Stroke and dementia

Outcome measures

Primary outcome

• The primary outcome measure is the cerebrovascular reactivity (CVR) as

determined by BOLD MRI (T2*) brain scan response to hypercapnic challenge at

the end of the 2 week run-in phase and after 4 weeks of monotherapy while still

on medication.

Secondary outcome measures:

• Mean systolic blood pressure (SBP) assessed by daily telemetric monitoring

within the last week of the run-in phase and within the last week of each

treatment phase

• Blood pressure variability (BPv) operationalized as coefficient of variation

(100*standard deviation (std)/mean SBP) across multiple measurements and

assessed by daily telemetric monitoring within the last week of the run-in

phase and within the last week of each treatment phase

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Study description

Background summary

Stroke and dementia rank among the most pressing health issues in Europe. Cerebral small vessel diseases (SVDs) have emerged as a central link between these two major co-morbidities. SVDs account for more than 30% of strokes and at least 40% of dementia. Despite this profound impact on human health, there are no treatments with proven efficacy against SVDs. Treat-SVDs is part of a coordinated programme to elucidate key mechanisms common to different SVDs, and determine how these mechanisms contribute to individual SVDs (SVDs@Target Project, funded by the European Horizon 2020 Scheme).

Recently, it has been proposed that endothelial dysfunction of microvessels plays a key role in the development of SVDs. Endothelial dysfunction in the brain can be measured by assessing blood flow response to a stimulus. This measure is termed cerebrovascular reactivity (CVR). CVR is known to be impaired after stroke as a marker for endothelium dysfunction.

Studying the effects of different antihypertensive drug classes on microvascular function, assessed by CVR and BPv, holds great promise for improving our mechanistic understanding of SVDs, stroke, and dementia. Currently there are no specific treatments to prevent the clinical or radiological progression of SVDs. Proving the feasibility of multi-centre, multinational trials using CVR and telemetric BP monitoring will be vital for proceeding to future, larger trials of new SVDs therapies

Study objective

Primary objective:
To test the hypothesis that the calcium channel blocker amlodipine has a superior beneficial effect on cerebrovascular reactivity in patients with symptomatic SVDs when compared to either the Angiotensin II type 1 (AT1) receptor blocker losartan or the beta-blocker atenolol.

Secondary objective:

To test the hypothesis that losartan has a superior beneficial effect on cerebrovascular reactivity when compared to atenolol

Study design

Treat-SVDs has a multicentre, multinational, prospective randomised, open-label, 3 sequence crossover study design with blinded endpoint assessment (PROBE)

Intervention

There are three different antihypertensive medicinal products used in this study:
• amlodipine 2.5 to 10 mg orally administered once daily
• losartan 25 to 100 mg orally administered once daily
• atenolol 25 to 100 mg orally administered once daily

Every patient will take three different antihypertensive medicinal products from three separate drug classes for four weeks, each with a different mechanism that affects the cerebrovascular reactivity.

Patients meeting eligibility criteria will be randomly allocated to one of three sequences of antihypertensive treatment:
Group 1: amlodipine > losartan > atenolol
Group 2: atenolol > amlodipine > losartan
Group 3: losartan > atenolol > amlodipine.

Study burden and risks

Participants will attend for 5 visits over a period of 14 weeks.

After enrolment participant have to stop taking their antihypertensive medication for the two weeks run-in period. During this run-in period there will be an increased risk for cardiovascular events and for hypertensive crisis. To counteract this, we
a) exclude patients taking more than two antihypertensive drugs
b) measure blood pressure regularly during the whole trial period
c) administer rescue medication as needed (and)
d) withdraw subjects in case of persisting hypertension despite antihypertensive treatment according to the trial protocol.

During the first visit (the screening), patients proceed to have a full medical history, physical examination will be performed, cognitive testing will be performed and blood samples will be taken for analysis. Participants receive a BP machine to perform home BP monitoring with the device 2-3 times daily for the next 14 weeks.

The visits next 4 visits take place from week two with an interval of 4 weeks. During the visits the patients undergo MRI with a CVR measurement. No contrast agent is used during the MRI scans. Total MRI time the first visit is 60 minutes divided in two sessions. The MRI during the next three visits takes 40 minutes. During every visit a physical examination is performed and blood samples will be taken for analysis.

The patients included in the trial are in need of an antihypertensive treatment due to hypertension or the secondary prevention of stroke. In both cases, the application of antihypertensive drugs is generally recommended and in line with clinical standards.
Every participating patient will take antihypertensive drugs belonging to three different drug classes with different impact on BPv. For the purpose of a personalised medicine, each patient participating in this trial will be informed which medication does have the highest benefit for lowering blood pressure. Trial participants will receive an individualised feedback on the development of his/her BP and on pulse wave analysis depending on the three different drugs.
The results of this trial will reveal new insights on the influence of different antihypertensive drugs in SVDs and will lead to a better understanding of SVDs. Based on the results of our trial, we aim to optimise treatment in patients with SVDs.

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

• Symptomatic SVD defined as
- a history compatible with clinical lacunar stroke syndrome in the last 5 years with a small subcortical infarct visible on MRI scan or CT scan compatible with the clinical syndrome
- or cognitive impairment defined as visiting a memory clinic with cognitive complains*, and capacity to and capacity to consent with confluent deep WMH on MRI (defined on the Fazekas scale as deep WMH score >= 2).
*concluded by the treating physician based on a validated cognitive measurement tool (for example but not limited to MoCA or CAMCOG)
-or a diagnosis of CADASIL (NOTCH 3 mutation carriers)

• Indication for antihypertensive treatment (as defined by meeting one of the following):
o Hypertension defined as SBP >=140mmHg or diastolic BP (DBP) >=90mmHg without antihypertensive treatment or use of an antihypertensive drug for previously diagnosed hypertension
o Prior history of stroke or transient ischaemic attack (TIA),
• Age 18 years or older, written informed consent

Exclusion criteria

• Inclusion criteria are not met,
• Unwillingness or inability to give written consent,
• Pregnant or breastfeeding women, women of childbearing age not taking contraception. ,
• Contraindications to MRI (pacemaker, aneurysm clip, cochlear implant etc.) ,
• Other major neurological or psychiatric conditions affecting the brain and interfering with the study design (e.g. multiple sclerosis), In case of clinical lacunar stroke other causes of stroke such as
o >=50% luminal stenosis (NASCET) in large arteries supplying the infarct area
o major-risk cardioembolic source of embolism (permanent or paroxysmal atrial

fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis)
o other specific causes of stroke (e.g. arteritis, dissection, migraine/ vasospasm, drug misuse) ,
• Other stroke risk factor requiring immediate intervention that would preclude involvement in the study,
• Renal impairment (eGFR <35 ml/min),
• Panic disorder,
• Life expectancy <2 years,
• Use of >2 antihypertensive drugs at maximum dose or equivalent (one drug at the maximum dose and two drugs at half of the maximum dose) for an appropriate BP control,
• Contraindications to the applied antihypertensive drugs as known
o Severe aortic stenosis
o Bilateral renal artery stenosis
o Severe arterial circulatory disorders
o Atrioventricular block II° or III° or sick sinus syndrome
o Heart failure (NYHA III or IV)
o Bradycardia, resting heart rate <50/min
o Bronchospastic diseases such as severe bronchial asthma
o Severe hepatic dysfunction such as liver cirrhosis
o Use of monoamine oxidase (MAO)-A-blockers
o Use of simvastatin >20mg/d
o Metabolic acidosis
o Disturbed electrolyte homeostasis such as hypercalcaemia, hypokalaemia, and hyponatraemia
o Symptomatic hyperuricaemia (gout)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	.
Generic name:	Amlodipine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	.
Generic name:	Atenolol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	.
Generic name:	Losartan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-03-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-10-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-06-2019

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2019
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	EUCTR2016-002920-10-NL
ClinicalTrials.gov	NCT03082014
CCMO	NL59984.068.17