Hypertensive treatment in elderly with cerebral small vessel disease: should we SPRINT faster?

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON47398

Source
ToetsingOnline

Brief title
Treatment of hypertension in elderly with CSVD

Condition

- Central nervous system vascular disorders
- Vascular hypertensive disorders

Synonym
Hypertension High Blood Pressure

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cerebral Bloof Flow (CBF), Cerebral Small Vessel disease (CSVD), Hemodynamics, Hypertension

Outcome measures

Primary outcome

The primary outcome measures are: CBF (static and dynamic) velocity measured

with Transcranial Doppler (TCD).

Secondary outcome

Secondary outcome measures are: cognitive functioning, degree of white matter

lesions. orthostatic hypotension, cerebral autoregulatory capacity, CO2

responsiveness, premature trial termination because of unacceptable drug side

effects.

Study description

Background summary

There is an ongoing dilemma for clinicians deciding which hypertensive treatment target should be used in hypertensive older patients. In recently developed recommendations for hypertension by the Eight Joint National Committee (JNC 8) got revised for patients 60 years and older, i.e. 150mmHg instead 140mmHg systolic BP (SBP) cut-off. These panel members published a minority report stating that the currently available evidence does not support new less stringent systolic cut-off values for older persons. Strikingly, the recently published SPRINT trial * a randomized trial of intensive versus standard BP control * confirmed their statement (Wright et al. NEJM 2015). The SPRINT trial showed that among adults, including those older than 70 years, lowering SBP to a target less than 120mmHg, as compared with the standard goal of less than 140mmHg, resulted in significantly lower rates of fatal and non-fatal cardiovascular events and death from any cause in the long term. So far, all available trials, including the SPRINT trial, mainly included healthy older participants with little or no co-morbidity, a healthy vascular system, and normal physical and cognitive functioning. It is not clear is these results can be translated to routinely daily practice in which doctors

encounter less healthy older subjects.
Under healthy physiologic conditions, blood flow to the brain is tightly regulated by a harmonized function of the systemic and cerebral circulation. This tight regulation aims to optimize the combination of blood flow and perfusion pressure at the tissue level to maintain adequate brain perfusion, despite fluctuations in systemic BP. With age cerebral blood flow (CBF) declines due to damage in the circulation and in particular the small vessels. Hence, higher perfusion pressures are necessary to maintain adequate brain perfusion. In patients with microvascular brain lesions, brain autoregulation becomes less efficient making the brain more dependent on systemic BP levels (Novak et al. Neurology 2003).
Although little evidence is available, an experimental study in diabetic patients showed a decline in CBF with more intensive BP control (Kim et al Hypertension 2011). The short-term effect of intensive BP control on CBF in patients with hypertension and cerebral small vessel disease has never been studied. Furthermore, the (long-term) effect of possible decreasing CBF is on cognition and cerobral vascular lesions, has never been studied before.

Study objective

The main objective of this effectiveness study is to test if intensive control (SBP *120 mmHg) decreases cerebral blood flow velocity compared to conventional targets (SBP<140-150 mmHg) in patients with CSVD and hypertension. Secondary objectives are to test the effect of tight blood pressure control on cognitive functioning, degree of white matter lesions, orthostatic hypotension, dynamic cerebral autoregulatory capacity, CO2 responsiveness, premature trial termination because of unacceptable drug side effects.

Study design

Randomized controlled intervention study.

Intervention

The intervention group will be treated using SPRINT-targets (SBP *120mmHg) and the control group using conventional blood pressure targets (SBP<140-150mmHg).

Study burden and risks

Patients will visit the Academic Medical Centre (AMC) Amsterdam twice (at baseline and at the end of the trial after 4 months) for several non-invasive measurements; Blood pressure will be measured continuously using finger-plethysmography (a small cuff wrapped around the middle finger). Continuous CBF velocity will be measured bilaterally with TCD at the middle cerebral artery in lying and standing position and
during repeated sit-stand manoeuvers. For this, patients will be wearing a head

band with external probes. Peripheral oxygenation will be measured using stickers on the patient's chest. Participants could experience some physical discomfort from the head band and/or chest stickers. During their first and second visits at the AMC, patients will be asked to perform the DSST, a neuropsychiological test on a computer which takes appr. 1-3 min. During their second visit the following cognitive tests will also be performed: Mini Mental State Examination (MMSE, questionnaire), the Stroop Color and Word Test (on a computer) and the 15 Words Memory Test (questionnair). A questionnaire assessing orthostatic complaints and falling will also be filled in. These tests take appr. 20 min in total to complete. The MMSE, 15 words memory test, Stroop test and the questionnaire assessing orthostatic complaints are performed at baseline during the standard work-up at the outpatient clinic.

During their 'treat-to-target-phase' patients will be asked to measure their blood pressure every two weeks during 3 consecutive days. Possible experiences symptoms and their blood pressure values will be written down in a personal diary. Two weeks after starting their antihypertensive treatment patients will be seen at the VUmc outpatient clinic to evaluate the therapy and their lab results. This is part of their 'regular care' and not an extra hospital visit/ blood sampling. During the following weeks patients will recieve a Phone call every 2 weeks to evaluate their treatment and necessarily adjust their drug regime. In case of drugs side-effects/complaints participants can contact assistant researcher dr. Emma Kleipool. She will contact the geriatrician on call. If she is not available, patients can contact the geriatrician who is on call directly. Every VUmc geriatrician is familiar with this trial. The geriatrician decides what further steps need to be taken (e.g. visit COGA outward patient clinic, visit to the emergency department, potential adjustments to/ discontinuation of antihypertensive medication). Adjustments to a patient*s treatment will not be based on the exact height of the diastolic blood pressure. Observational studies suggest that diastolic BP levels below 70 mmHg are associated with an increased mortality risk in the oldest old (80 years and older) (Mattila et al. 1988, Satish et al. 2001). However, it is unclear if low diastolic BP is a risk factor for mortality or if it is an indicator of co-morbidity of frailty and therefore associated with a lower survival. However, in intervention studies, this observation has not been replicated.

No extra blood samples will be taken and no extra physical examination will be performed.

The risk to and burden for the subject will be moderate. Patients could experience symptoms related to decreasing blood pressure (head ache, dizziness, orthostatic complaints) with an accompanying increased of falling. Furthermore, acute decreasing kidney function, eletrolyte disorders and drug specific side effects such as a dry cough (ACE-inhibitor), bradycardia (betablocker calcium channel blicker), ankle oedema (calcium channel blocker). However, blood pressure treatment will be done in a controlled matter supervised by a

geriatrician based on systolic blood pressure ánd drug side effects. In case of experiencing unacceptable side effects, blood pressure will not be loweredany further. Antihypertensive drugs will be discontinued or the dose will be lowered in order to achieve blood pressure targets at which the patients does not experience these symptoms. Considering these actions, negative effects of blood pressure will be avoided as much as possible.

Contacts

Public
Vrije Universiteit Medisch Centrum

Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

Boelelaan 1117
Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- * 65 years of age
- High systolic blood pressure of 150-200 mmHg assessed with a daytime 24-hour BP (with or without taking antihypertensive medication)

- Cerebral small vessel disease (white matter lesions; Fazekas score * 2) on MRI

Exclusion criteria

- Diabetes mellitus
- Experienced myocardial infarction within the past 12 months
- Medical history of stroke in the past 6 months or large (sub) cortical cerebral infarction on MRI
- Medical history of end stage heart failure (NYHA III-IV)
- Stage 4-5 kidney failure
- Clinical Dementia Rating (CDR) scale>1
- Life expectancy less than 1 year
- Unable to obtain an optimal window for TCD measurements
- Significant stenosis (>70%) of the left of right common carotid artery

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO Date:	19-06-2017

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
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
CCMO	NL59947.029.17