Research protocol

**Effects of temporary discontinuation of antihypertensive treatment in older patients with cognitive impairment: a randomised controlled trial.**

The Dante Study Leiden

Discontinuation of ANti hypertensive Treatment in the Elderly
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**Trialregister**
This study is registered with ClinicalTrials.gov, number @@@
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List of abbreviations and relevant definitions

CME        Committee Medical Ethics
DANTE      Discontinuation of ANti hypertensive Treatment in the Elderly
DSMB       Data Safety Monitoring Board
GARS       Groningen Activity Restriction Scale (general daily functioning)
GP         General Practitioner
LDST       Letter-Digit Substitution Test (psychomotor speed)
LEON       Leids Eerstelijns Onderzoeksnetwerk (Leiden Primary Care Research Network).
LUMC       Leiden University Medical Center
MMSE       Mini Mental Status Examination
NPI        Neuropsychiatric Inventory (neuropsychiatric symptoms)
SCWT       Stroop-Colour Word Test (executive functioning)
TMT        Trail Making Test (executive functioning)
VAT        Visual Association Test (immediate and delayed) picture memory
15-WVLT    15-Word Verbal Learning Test (immediate and delayed) verbal memory
1. Summary

Background: Low blood pressure in old age may compromise cerebral perfusion, which may increase the risk of cognitive impairment, depressive symptoms, and apathy. Cerebral imaging studies have shown that cerebral blood flow is reduced in areas of small vessel disease and that the degree of hypoperfusion correlates with disease severity. Hence, blood pressure reduction in older people may lead to hypoperfusion, especially in patients with cerebral small vessel disease, resulting in increased mental health problems like cognitive impairment, depression, and apathy.

Objectives: To assess whether temporary discontinuation of antihypertensive therapy in mildly cognitively impaired older patients on antihypertensive treatment improves cognitive and psychological functioning.

Study design: Randomized non-blinded controlled clinical trial.

Study population: Patients ≥ 75 years on antihypertensive treatment with mild cognitive impairment.

Selection criteria and recruitment: All 400 patients will be recruited from LEON (Leids Eerstelijns Onderzoeksnetwork [Leiden Primary Care Research Network]) and the Memory Clinic (LUMC). Inclusion criteria are (1) age ≥ 75 years, (2) current antihypertensive treatment, (3) current systolic blood pressure < 160 mmHg, and (4) Mini-Mental State Examination (MMSE) score ≥ 21 and ≤ 27. Exclusion criteria are: a history of myocardial infarction, stroke, coronary reperfusion procedures (CABG/PCI), or heart failure requiring antihypertensive medication.

Sample size: The difference in the cognitive compound score between the intervention and control group is estimated to be 0.3 (SD 1.0). With an alpha of 0.05 and a power of 0.80, we calculate that 175 patients are needed in each group. Assuming a drop-out rate of 10% in each group (due to mortality and refusal to further participate), a total number of 200 patients will be included in each arm of the trial.

Intervention: Patients will be randomized to either continuation (n=200) or discontinuation (n=200) of antihypertensive treatment. Discontinuation of antihypertensive medication by patients’ own general practitioner may vary from abrupt and complete discontinuation to gradual and partial discontinuation, with a 20 mmHg increase in systolic blood pressure as target and 180 mmHg as maximum systolic blood pressure. For the various antihypertensive drugs commonly used by older people a discontinuation algorithm will be used. Discontinuation will be executed and completed within four weeks from randomization for a period of three months thereafter. All patients in both arms of the trial will receive regular blood pressure measurements by the GP during the first month after randomisation and thereafter at home by the research personnel in order to make both treatment arms as similar as possible.

Outcome measures: Primary outcome is the change in the compound cognitive score between baseline and follow-up at 4 months after randomisation;
secondary outcomes are the changes in the four separate cognitive domains (global cognitive functioning, executive functioning, memory and psychomotor speed); depressive symptoms, apathy, daily functioning, and quality of life between baseline and follow-up.

**Instruments:** In all patients a number of cognitive measurements will be obtained: MMSE for global cognitive functioning, Stroop-Colour Word Test (SCWT) and Trail Making Test (TMT) for executive functioning, 15-Word Verbal Learning Test (15-WVLT) and Visual Association Test (VAT) for (immediate and delayed) verbal and picture memory, and Letter-Digit Substitution Test (LDST) for psychomotor speed. Moreover, the Neuropsychiatric Inventory (NPI) will be carried out for, among others, assessment of depression and apathy. Furthermore, general daily functioning (Groningen Activity Restriction Scale) and quality of life (Cantril’s ladder) will be measured. The presence and degree of small vessel disease will be assessed based on an 3 Tesla MRI examination. Anatomical, functional as well as hemodynamic parameters will be obtained.

**Burden, risks and benefit associated with participation:** Patients have to come to the LUMC for the MRI-scan. Assessments of cognitive functioning and mental wellbeing (2 hours) will be done at the patients’ home both at baseline and at 4 months follow-up. Patients in both study arms will continue to receive monthly blood pressure measurements at home by research personnel during follow-up after a stable blood pressure has been reached at baseline. This will be done for safety reasons in the discontinuation arm and to make both study arms as similar as possible also in the stop arm. Patients in the discontinuation arm will be put on their original antihypertensive medication when systolic blood pressure exceeds 200 mmHg or diastolic blood pressure exceeds 110 mmHg. Moreover, all cardiovascular events during the study will be closely monitored to prevent an increase in cardiovascular events in the discontinuation group. A Data Safety and Monitoring Board (DSMB) will be installed for monitoring of the safety data (cardio- and cerebrovascular events) and stopping rules will be formulated. Given the future rise in the number of older people in our society, the impact of this project will be enormous when we demonstrate that a substantial proportion of cognitive impairment and associated psychiatric symptoms in older patients can be alleviated by discontinuation of antihypertensive therapy.
2. Background and rationale
The number of elderly in our society has risen enormously over the past decades and their numbers will continue to rise the coming years (Oeppen et al., 2002). With these increasing numbers of older people, the prevalence of dementia will rise too. The incidence of dementia increases from less than one per 1000 person years in patients aged 60 years to more than 20 per 1000 person years in patients aged 80 years and over (Ott et al., 1998). A similar increase with age has been observed for the incidence of depressive symptoms and apathy (Beekman et al., 1999; Onyike et al., 2007). Cognitive impairment, depression and apathy often concur, suggesting a close relation between them (Vinkers et al., 2004). Hence, the coming decades a substantial increase is expected in total number of older people with dementia and accompanying psychiatric symptoms such as depression and apathy.

The last decades have also shown an increase in treatment of high blood pressure. Numerous studies have shown beneficial effects of blood pressure lowering on morbidity and mortality. This has resulted in an increased awareness of the possible deleterious effects of high blood pressure. However, high blood pressure in old age might not always be deleterious or might even be beneficial. For example, patients from the Leiden 85-plus Study with high blood pressure did not have an increased risk of mortality, whereas 85-year-old patients with low systolic and diastolic blood pressure even had an increased mortality risk (van Bemmel et al., 2006). Similar observations have been reported in other elderly populations (Heikinheimo et al., 1990; Lernfelt et al., 2002; Molander et al., 2008; Kagiyama et al., 2009).

The impact of blood pressure lowering on cognitive function is less clear. In 1998, the Syst-Eur trial showed that blood pressure lowering with the calcium antagonist nitrendipine reduced the incidence of dementia in the elderly with 50% (Forette et al., 1998). This lowering of incidence of dementia could not be replicated in the recent HYVET-COG trial, which demonstrated that blood pressure lowering with a diuretic and, if necessary, an ACE inhibitor (indapamide and perindopril) did not result in cognitive benefits in elderly aged 80 years and over (Peters et al., 2008). A likely explanation for the absence of cognitive effects of blood pressure lowering in the HYVET-COG trial is that in high age, when cerebral small vessel disease is more prevalent, a higher blood pressure is required to overcome the increased resistance of narrowed cerebral arterioles to guarantee adequate cerebral perfusion. Indeed, in a study among patients who visited our memory clinic, we found an association between hypertension and improved cognitive function in patients with radiological evidence of small vessel disease (van Vliet et al., 2010). In a combined analysis of data of the Rotterdam Study and the Leiden 85-plus Study, we have shown that the impact of hypertension on cognitive function is influenced by age (Euser et al., 2009). In people younger than 75 years both high systolic and high diastolic blood pressures were related to worse cognitive functioning ten years later. This association was absent in people between 75 and 85 years and was even reversed in people aged 85 years and over. In the oldest old both high systolic and high diastolic blood pressure were related to a better cognitive function during five years of follow-up. Furthermore, among older subjects (mean age 67 years) low blood pressure was associated with presence of depressive symptoms.
in both older subjects who were treated for hypertension and those who were not (Ng et al., 2010).

A high blood pressure in old age may be required to maintain adequate cerebral perfusion. Low blood pressure in old age may compromise cerebral perfusion, which may increase the risk of cognitive impairment, depressive symptoms, and apathy (Birns et al., 2005). Cerebral imaging studies have shown that cerebral blood flow is reduced in areas of small vessel disease and that the degree of hypoperfusion correlates with disease severity (O'Sullivan et al., 2002). Apart from vascular narrowing, small vessel disease is also characterized by destruction of the smooth muscle cells in the media of arterioles, which has a profound effect on the cerebrovascular autoregulation. In small vessel disease, deterioration of this autoregulatory capacity further increases the permanent dependency of the brain on adequate blood supply. In line with this idea we found significant better cerebral blood flow in participants of the Leiden 85-plus Study with an excellent cognitive function compared to a group of elderly with dementia (Spilt et al., 2005).

Hence, blood pressure reduction in older people may lead to hypoperfusion, especially in patients with cerebral small vessel disease, resulting in increased mental health problems like cognitive impairment, depression, and apathy. In this study we will assess whether temporary discontinuation of antihypertensive therapy in mildly cognitively impaired older patients on antihypertensive treatment improves cognitive and psychological functioning.

3. Study objectives
The primary objective of this study is to assess whether temporary discontinuation of antihypertensive therapy in mildly cognitively impaired (MMSE score ≥ 21 and ≤ 27) older patients on antihypertensive treatment improves cognitive function as assessed by a compound score of six cognitive tests. Secondary objectives are to assess (1) whether discontinuation of antihypertensive therapy improves the separate cognitive domains of global and executive functioning, immediate and delayed memory, and psychomotor speed (2) whether it reduces the occurrence of accompanying psychiatric symptoms, like depression and apathy, (3) whether it improves general daily functioning and quality of life, and (4) whether patients with radiological evidence of small vessel disease show the largest clinical benefit in cognitive performance and associated psychiatric symptoms.

We hypothesize that discontinuation of antihypertensive therapy in mildly cognitively impaired patients aged 75 years and older will improve their cognitive impairment, depressive symptoms, apathy, general daily functioning and quality of life in comparison with older patients who continue their antihypertensive treatment. We also think that these effects will be larger in older patients with cerebral MRI evidence of small vessel disease.

4. Study design
A randomised, controlled clinical trial to assess whether temporary discontinuation of antihypertensive therapy for three to four months improves
cognitive function and associated psychiatric symptoms like depression and apathy in patients aged 75 years and over.

5. Study population
5.1 Patients
Patients aged \( \geq 75 \) years on antihypertensive treatment with mild cognitive impairment.

5.2 Selection criteria
5.2.1 Inclusion criteria are (1) age \( \geq 75 \) years, (2) current antihypertensive treatment with a calcium antagonist, beta-blocker, diuretic, ACE-inhibitor, or angiotensin-II-receptor blocker, (3) current systolic blood pressure < 160 mmHg for patients without a history of cardiovascular disease (defined as myocardial infarction, coronary reperfusion procedures (CABG/PCI), peripheral artery disease, claudicatio intermittens) or without diabetes, or systolic blood pressure < 140 mmHg for patients with a cardiovascular event (defined as myocardial infarction, CAGB, PTCA, peripheral artery disease, claudicatio intermittens) more than 3 years ago or diabetes, and (4) Mini-Mental State Examination (MMSE) score between 21 and 27.

5.2.2 Exclusion criteria are a history of stroke or TIA, or heart failure requiring antihypertensive medication and/or a clinical diagnosis of dementia.

5.3 Sample size
Sample size calculation is based on the main outcome measure, the change in the cognitive compound score between baseline and follow-up. The difference in the cognitive compound score between the intervention and control group can be given as an effect size since the score is normally distributed around zero with a standard deviation of one. There is no information available in the literature to reliably predict what the actual effect size will be. Hence, a power calculation is a hazardous. But if we assume that the effect size is 0.3 (SD 1.0), which is a moderate effect (Cohen, 1988), we calculate that 175 patients are needed in each group, using an alpha of 0.05 and a power of 0.80. Assuming a drop-out rate of 10% in each group (due to mortality and refusal to further participate), a total number of 200 patients will be included in each arm of the trial.

6. Methods
6.1 Intervention, randomisation and intervention allocation
Patients will be randomised in a 1:1 ratio to either continuation \( (n=200) \) or discontinuation \( (n=200) \) of antihypertensive treatment using a stratified block randomization, stratified for type of antihypertensive treatment in 2 strata. Concealment of treatment allocation will be ensured by a central computerized randomization procedure. Patients and research personnel can not be blinded to treatment allocation. Research nurses who are responsible for baseline and follow-up measurements, will be kept unaware of treatment allocation. Blood pressure lowering will be carried out by the patients’ own general practitioner, which will minimize the possibility that information bias will affect the assessment of outcome measures.

6.1.1 Antihypertensive medication discontinuation algorithm
Discontinuation of antihypertensive medication by patients’ own general practitioner may vary from abrupt and complete discontinuation to gradual and partial discontinuation, with a 20 mmHg increase in systolic blood pressure as target and 180 mmHg as maximum systolic blood pressure. For the various antihypertensive drugs commonly used by older people a discontinuation algorithm have been developed (see appendix 1). Discontinuation will be executed and completed within four weeks from randomization by patients’ own general practitioner. Internists of the LUMC Department of Gerontology and Geriatrics will assist general practitioners in advising blood pressure lowering algoritm.

6.2 Study procedures, recruitment and informed consent procedure (figure 1)
The 400 patients will be recruited from the LEON (Leids Eerstelijns Onderzoeksnetwerk [Leiden Primary Care Research Network], regio noordelijk Zuid-Holland) and from the Memory Clinic LUMC. All participating GP’s will sign a 'lokale uitvoerbaarheidsverklaring’.

In every standard general practice of 2350 patients, 113 (4.8%) patients aged ≥ 75 years are available, of whom 54 (2.3%) have no serious vascular disease, of whom 24 (1%) use antihypertensive medication, and 14 (0.6%) have a systolic blood pressure < 160 mmHg at their last visit to the GP. It is known from earlier research (ISCOPE) that of these patients, 7 (0.3%) will have an MMSE-score ≥ 21 and ≤ 27, resulting in 7 possibly eligible patients per standard general practice. Taking into account a refusal and drop-out rate of 40%, this means that around 400:4= 100 general practices have to be included for this study. Within these general practices, all patients 1. aged ≥ 75 years; 2. who use antihypertensive medication (a calcium antagonist, beta-blocker, diuretic, ACE-inhibitor, or angiotensin-II-receptor blocker) for hypertension; 3. whose last systolic blood pressure was < 160 mmHg; and 4. who have possibly mild cognitive impairment according to the general practitioner, will be selected from the electronic medical record and asked to participate by their general practitioner (GP). Patients with a history of myocardial infarction and coronary reperfusion procedures (CABG/PCI) < 3 years, stroke, heart failure requiring antihypertensive medication and/or a clinical diagnosis of dementia will be excluded. The GP assesses the MMSE of the selected patients, and in case of an MMSE-score ≥ 21 and ≤ 27, explains the procedure of the trial and provided the patient with an information leaflet.

All patients fulfilling the selection criteria and agreeing to participate, are reported by the GP to the research centre. Within one week an independent researcher will contact the patient to make an appointment at the patients’ home. During this home visit, further explanation about the study will be given to the patient and to a close relative of the patient (as a prox decision maker) and written informed consent will be obtained (see also paragraph on ethical considerations). After informed consent, baseline information and BP will be gathered, and baseline Neuropsychological Examination, Neuropsychiatric Inventory, general daily functioning and quality of life will be assessed.

Within one week from these baseline-assessments, a MRI-scan will be done at the LUMC, whereafter patients will be randomized to either continuation or
discontinuation of antihypertensive treatment. The GP will be informed by the research centre about the outcome of randomisation. Within four weeks from randomisation discontinuation will be executed and completed by patients’ own general practitioner, strictly according to discontinuation protocol, targeting at an increase of 20 mmHg in systolic blood pressure, with a maximum of 180 mmHg blood pressure (see appendix 1). During the discontinuation period of a month blood pressure will be monitored weekly until a stable blood pressure has been reached. Thereafter, patients in the discontinuation arm will continue to receive regular blood pressure measurements according to protocol for safety monitoring. Four months after randomisation, all patients will be visited again at home by the researcher for assessment of all outcome measures. The GP will decide whether or not antihypertensive treatment will be started again in the patients of the discontinuation group.

6.3 Outcome measures

6.3.1 Primary outcome measure
At baseline and at 4 months follow-up, from all patients a number of cognitive measurements will be obtained: MMSE (Folstein et al., 1975) for global cognitive functioning, Stroop-Colour Word Test (SCWT) and Trail Making Test (TMT) for executive functioning, 15-Word Verbal Learning Test (15-WVLT) and Visual Association Test (VAT) for (immediate and delayed) verbal and picture memory, and Letter-Digit Substitution Test (LDST) for psychomotor speed (Lezak et al., 2004). The six aforementioned cognitive tests will be combined in a cognitive compound score (Kalmijn et al., 2002). Where appropriate, test results will first be transformed to obtain normal distributions. Then raw data will be made comparable by transforming them into a standardized z score (the difference between each test score and the average score, divided by the standard deviation of that score). The change in the cognitive compound score between baseline and follow-up will be the primary outcome measure.

6.3.2 Secondary outcome measures
At baseline and at 4 months follow-up, moreover, the Neuropsychiatric Inventory (NPI) will be carried out for, among others, assessment of depression and apathy (Cummings et al., 1994). Furthermore, general daily functioning will be assessed with the Groningen Activity Restriction Scale (GARS) (Kempen et al., 1996) and quality of life with Cantril’s ladder (Cantril, 1965). Secondary outcome measures are the change in the four separate cognitive domains (global cognitive functioning, executive functioning, (immediate and delayed) memory and psychomotor speed; the change in depressive symptoms and apathy as assessed with the NPI; physical functioning as assessed with the GARS, and quality of life according to Cantril’s ladder.

6.4 Safety aspects

6.4.1 Adverse and serious events
All cardiovascular events (myocardial infarction, heart failure, stroke) during the study will be closely monitored to prevent an increase in cardiovascular events in the discontinuation group. All patients in both arms of the trial will receive blood pressure measurement every two weeks by their GP during the first month after randomisation. Thereafter, monthly blood pressure measurements will be done
by the research personnel at the patient’s home, for safety monitoring in patients in the discontinuation arm and to make both study arms as similar as possible also in the stop arm. Patients in the discontinuation arm will be put on their original antihypertensive medication when systolic blood pressure exceeds 200 mmHg or diastolic blood pressure exceeds 110 mmHg. All adverse events will be reported to the Committee Medical Ethics (CME) LUMC.

6.4.2 Data Safety and Monitoring Board (DSMB) and stopping rules
A Data Safety and Monitoring Board (DSMB) will be installed for monitoring of the safety data (cardiovascular events). Stopping rules will be formulated.

6.5 Instruments
6.5.1 Cognitive measures
Mini Mental State Examination (Folstein et al., 1975)
The MMSE that consists of 11 items has been found to be reliable and valid in assessing global cognitive function. Scoring range of the MMSE is 0 – 30 points with lower scores indicating worse global cognitive performance.

Stroop-Colour Word Test (Lezak et al., 2004)
The Stroop-ColourWord Test examines a person’s sustained attention in three conditions: colour naming, word reading, and naming the colour of the ink of an incongruous colour name (interference). For each condition the patient has 45 seconds and the total of all right answers is scored, with maximum 100 points per condition.

Trail Making Test (Lezak et al., 2004)
Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the ‘trail’. Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment. In this study, the TMT B minus TMT A score (s) will be used.

15-Word Verbal Learning Test (Lezak et al., 2004)
Immediate and delayed recall verbal memory is determined with the 15-WVLT. In this test 15 words are verbally presented, and the patient is asked to recall the presented words. This procedure is carried out three times. After twenty minutes, the patient are asked to recall the presented words again. Outcome for the immediate recall memory is the total number of correctly recalled pictures during the three procedures, and possible scores range from 0 to 45 words. Outcome for the delayed recall memory is the total number of correctly recalled pictures after 20 minutes, and possible scores range from 0 to 15 words. Lower scores indicate worse verbal memory.

Visual Association Test (Lezak et al., 2004)
The Visual Association Test is a brief learning task based on the visual association method, a classical memory aid. The test consists of cards with drawings and has three administration forms: form A and parallel form B are used for testing elderly patients. Both have six cue cards and six association cards. The VAT yields a total score in the range 0 – 100. Lower scores indicate worse picture memory.

**Letter-Digit Substitution Test (Lezak et al., 2004)**
The SDMT examines attention, working memory, visuoverbal substitution and motor speed, thus psychomotor speed. Patients have 90 seconds to write down the number that matches each of the geometric figures, which are printed on several lines.

6.5.2 Psychiatric measures
**Neuropsychiatric Inventory (Cummings et al., 1994).**
The NPI is a 10-20 minutes interview, that examines a wide range of neuropsychiatric symptoms, thereby recording severity and frequency separately. Next to depression and apathy, the NPI consists of the following behavioral domains: delusions, hallucinations, agitation, anxiety, euphoria, disinhibition, irritability, aberrant motor behavior, night-time behaviors, and appetite and eating disorders. For each domain there are four scores: frequency, severity, total (frequency x severity, with a maximum score of 12 points per item, and 144 in total), and caregiver distress (on a scale from 1-5 with higher scores indicating more stress).

6.5.3 Measures for daily functioning and quality of life
**Groningen Activity Restriction Scale (Kempen et al., 1996)**
The GARS examines disability in daily functioning. The GARS consists of 11 items that measure problems with Activities of Daily Living (ADL), such as ‘Can you dress yourself?’ and 7 items that measure problems with Instrumental Activities of Daily Living (IADL), such as ‘Can you do the shopping?’. The total GARS score ranges from 18-72 points, with higher scores indicating more difficulties with activities of daily living (Suurmeijer et al., 1994).

**Cantril’s ladder (Cantril, 1965).**
Satisfaction with life was measured by Cantril’s ladder that has steps numbered from 0 to 10 (Von Faber et al., 2001). Patients are asked to rate their present overall satisfaction with life on this ladder, resulting in scores from 0 (low satisfaction) to 10 (high satisfaction).

6.5.4 MRI examination
At baseline, the presence and degree of small vessel disease will be assessed in all participants based on an a 3 Tesla whole body scanner MRI examination that will be performed at the LUMC. Anatomical, functional as well as hemodynamic parameters will be obtained. Anatomical data include measurements of cortical thickness and localized cerebral atrophy determined on high resolution 3D-T1 weighted MRI. Moreover, the location and extent of white matter hyperintensities (on FLAIR) and microbleeds (on T2*-susceptibility weighted imaging) will be determined. Chronic and acute ischemic lesions will be characterized by diffusion weighted MRI. Functional data will be obtained by resting state MRI. By using independent component analysis, functional connectivity in the major cerebral
networks will be assessed. The haemodynamic status of the brain will be assessed by quantitative blood flow measurements in the major feeding arteries to the brain and regional cerebral blood flow (rCBF) will be measured on parenchymal level using continues arterial spin labelling. All MRI measures will provide us with various indicators of cerebral brain damage to assess the interaction between blood pressure and cognitive functioning.

7. Data analysis
The six cognitive tests will be combined in a cognitive compound score (Kalmijn et al., 2002). Where appropriate, test results will first be transformed to obtain normal distributions. Then raw data will be made comparable by transforming them into a standardized \( z \) score (the difference between each test score and the average score, divided by the standard deviation of that score). The change in the cognitive compound score between baseline and follow-up will be the primary outcome measure. Secondary outcome measures are the change in the following separate cognitive domains: global cognition, executive functioning, memory and psychomotor speed; and the change in depressive symptoms, apathy, physical functioning, and quality of life.

In the statistical analysis we will employ the intention-to-treat approach, except for the etiological research questions on the interaction between MRI-parameters of small vessel disease and blood pressure increase on cognitive functioning and mental health measures. For those research questions a per protocol analysis will be employed. Descriptive, univariate and multivariate analyses will be used for comparison of the control and experimental older patients. No interim analysis has been planned. A DSMB will monitor the safety data (myocardial infarction, heart failure, stroke, death).

8. Ethical considerations
8.1 Regulation statement
The study will be done in accordance with Good Clinical Practice guidelines, the declaration of Helsinki (version 2008) and the Medical Research Involving Human Subjects (WMO).

8.2 Recruitment and informed consent
The 400 patients will be recruited from the LEON (Leids Eerstelijns Onderzoeksnetwerk [Leiden Primary Care Research Network], regio noordelijk Zuid-Holland) and from the Memory Clinic LUMC. If a general practice is not a member of the LEON, a ‘lokale uitvoerbaarheidsverklaring’ will be signed (see for further details on recruitment procedures paragraph 6.2).

Patients will only participate in this study after they have signed an informed consent declaration. On this informed consent form they are also able to indicate whether or not they can be approached in the future. Participation is completely voluntarily and patients will be neither pressured nor be offered money for their participation, except for travel expenses, which will be covered. Participants are able to stop their participation at any time without adverse consequences, and will be explicitly told so. An independent physician, drs J.W. Blom, LUMC, will be available throughout the project for questions and advice.
We realise that our research involves patients who are possibly (partially) incompetent to decide whether or not to participate in the study. However, we firmly believe that there is no other group of patients in which the research question can be answered and that there is a chance that participation in the study may benefit the research patient (art. 4 lid 1 WMO).

Of course, every care will be taken in the informed consent procedure to explain the study in a way that is understandable for the older patient involved. Also, we strive to involve a close relative, who might act as proxy (surrogate) decision maker, both at the beginning and during the study. Individual considerations like the expected willingness to undergo the MRI examination will be taken into account when the patient is less able to decide for himself. During the study well-being of incompetent patients and the willingness to participate, as shown in reactions of incompetent patients, is taken as an important criterion for the decision whether or not to continue. During the course of the study the department of Medical Ethics and Health Law of the LUMC (prof. mr. dr. D.P. Engberts, dr. D.P. Touwen) will be available as consultants on ethical matters in general and concerning the informed consent procedure and the involvement of family members/proxy decision makers in particular.

Furthermore, a separate add-on ethical study will address the following research questions: 1. How do relatives reach a decision on whether or not to participate in a study, when the patient suffers from decreased cognitive and decisional abilities? and 2. What is the relation between the assessment of the decisional competency of the patient by his relative present at the informed consent conversation, and the MMSE score of the patient? (see addendum 12).

If the MRI shows accidental pathological findings, the neuroradiologists and neurologist will advice the general practitioner about the further strategy, who will inform the patient.

8.3 Compensation for injury
Patients are insured by a no-fault insurance of the LUMC. The investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

8.4 Incentive and travel expenses
Patients will be compensated for their travel expenses.

9. Administrative aspects and publication
9.1 Handling and storage of the data
All study data will be handled confidentially and anonymously. In order to ensure privacy, all patient data will be coded and these codes will be used in further data analysis. Only the principal investigators (R.C. van der Mast and A.J.M de Craen) will have access to the key of these codes and to the original documents. The originals of all source documents will be stored for a period of 15 years after report of the study has been finalized, after which all study-related documents will be archived on an external hard disk for 15 years. The handling of personal data complies with the Dutch Data Protection Act.

9.2 Amendments and add-on studies
Substantial amendments and add-on studies will be notified to the Medical Ethical Committee (CME). An add-on ethical study on the informed consent procedure involving proxi (surrogate) decision makers has already been designed and planned (see addendum 12).

9.3 Annual and end of study reports
A summary of the annual progress and end of study will be reported to the CME and ZonMw. Information will be provided on the date of inclusion of the first patient, the numbers of patients that were included and that completed the study, adverse events, and on other relevant information.

9.4 Public disclosure and publication policy
The identity of the participating patients will not be disclosed in any way in study publications. All results will be published in peer-reviewed national and international medical journals and presented on international conferences and congresses. Regarding the content of the publications, no agreements are or will be made with others than the participating departments of the LUMC.

10. References
11. Appendices

12. Add-on ethical study