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**Title:** Blood pressure in old age: exploring the relation with the structure, function and hemodynamics of the brain
**Issue Date:** 2016-09-06
Chapter 1

General introduction
Blood pressure in old age

With increasing age both systolic and diastolic blood pressure increase and, subsequently, the prevalence of hypertension rises. Hypertension, defined as a systolic blood pressure of 140 mmHg and above or a diastolic blood pressure of 90 mmHg and above, affects 75% of persons aged 65 years and over. Generally speaking, systolic blood pressure tends to continue to rise until age 75 years and decreases thereafter, whereas diastolic blood pressure tends to decrease after 70 years.

Blood pressure and cognition

The incidence of dementia increases from less than 1 per 1000 person-years in those aged 60 years, to more than 20 per 1000 person-years in individuals aged 80 years and over. High blood pressure is a major risk factor for dementia and cognitive decline. However, both high and low blood pressure have been linked to dementia and cognitive impairment and epidemiological studies show that the association between blood pressure and cognitive decline is age-dependent. High blood pressure at age 70 years is associated with cognitive impairment and is predictive of dementia 10 to 15 years later. Nevertheless, observational studies in older persons have suggested that a lower rather than a higher blood pressure is associated with incident dementia. The age at which the association between blood pressure and cognitive functioning is supposed to reverse is thought to be around 75 years. However, it remains unclear whether low blood pressure is a cause or a consequence of cognitive decline.

Results of placebo-controlled double-blind clinical trials that assessed the impact of the lowering of blood pressure on cognitive function in older persons are inconclusive. The Systolic hypertension in Europe (Syst-Eur) trial showed that lowering of blood pressure reduced the incidence of dementia by 55% in persons aged 60 years and over. However, this result was not replicated in the recent Hypertension in the Very Elderly trial (HYVET) trial, which demonstrated that blood pressure lowering did not result in cognitive benefits in persons aged 80 years and over. In addition, a meta-analysis of placebo-controlled double-blind clinical trials, that included the Syst-Eur and HYVET trial and comprised 15,936
hypertensive patients without apparent prior cerebrovascular disease, found no evidence for the prevention of incident dementia by use of antihypertensive treatment.\textsuperscript{18} Importantly, it has been pointed out that the participants of these trials were generally healthier than others of their age as was shown, for example, in the HYVET population, by the relatively low number of cardiovascular risk factors and co-morbidities.

Blood pressure and cerebral small vessel disease

Cerebral small vessel disease involves thickening of the vessel walls of the penetrating arterioles that supply the deep white matter in the brain with blood. Cerebral small vessel disease can be recognized on an MRI scan of the brain as white matter hyperintensities,\textsuperscript{19} microbleeds,\textsuperscript{20} and lacunar infarcts.\textsuperscript{21} The presence of cerebral small vessel disease is prognostic for future cognitive decline.\textsuperscript{21-24} Long-standing high blood pressure damages the cerebral vessels through hemodynamic stress and increases the risk for cerebral small vessel disease.\textsuperscript{25} There is increasing evidence that, particularly older persons with hypertension and overt signs of cerebral small vessel disease, are at increased risk of cognitive decline when subsequently exposed to lower blood pressure.\textsuperscript{26,27}

Pathophysiology underlying the association between blood pressure and cognition

Different pathophysiological mechanisms have been proposed to underlie the possible association between low blood pressure and cognitive decline. Because of the high metabolic demand of the brain a sufficient blood supply is essential for cerebral functioning. Neurovascular autoregulation mechanisms maintain a stable cerebral perfusion, despite variations in blood pressure.\textsuperscript{28} When blood pressure rises or falls, the cerebral arterioles constrict or dilate to maintain adequate cerebral perfusion.

In older persons, longstanding hypertension earlier in life and/or the presence of cerebral small vessel disease gives rise to narrowing of the arteriolar lumen. Once these cerebral arterioles are damaged, neurovascular autoregulation may react
insufficiently to variations in blood pressure levels. This renders the brain more vulnerable to hypoperfusion due to low blood pressure and leads to ischemia and tissue damage.\textsuperscript{27,28} Therefore, low blood pressure levels might result in cerebral hypoperfusion, particularly in older people with a history of cardiovascular disease and/or hypertension, and thus exacerbate cognitive decline.\textsuperscript{11,26,29} Consequently, in these older persons (intensive) treatment of hypertension may compromise cerebral blood flow and cause undesired consequences.

Aims of the study

The aim of the work in this thesis is to explore the role of blood pressure in relation to cerebral structure, neurocognitive function and hemodynamics of the brain in old age. For this purpose, the primary objective of this thesis is to assess whether discontinuation of antihypertensive therapy (thereby increasing blood pressure) in older persons with mild cognitive deficits and using antihypertensive medication, improves their cognitive and psychological functioning. Secondary objectives are to investigate the association of blood pressure with brain structure and cerebral microstructural integrity in older persons and to determine whether blood pressure is associated with cerebral blood flow. Further, we assessed whether cerebral microstructural integrity and grey matter covariance brain networks are associated with cerebral small vessel disease and with cognitive functioning in older persons.

The DANTE study Leiden

In June 2011, the Discontinuation of ANti hypertensive treatment in Elderly people (DANTE) Study Leiden was started. The DANTE Study Leiden was a community-based randomized clinical trial designed to explore whether discontinuation of antihypertensive treatment for four months would improve cognitive and psychological functioning. Individuals aged 75 years and over, with mild cognitive deficits (Mini-Mental State Examination score 21-27), without severe cardiovascular disease and all receiving antihypertensive treatment, were enrolled from 128 general practices in the DANTE Study Leiden. In a population of 385 older persons aged 75 to 96 years, blood pressure as well as cognition,
symptoms of depression and apathy, general daily functioning and quality of life were assessed at baseline and at four-month follow-up. In addition, MRI scans were performed at baseline in order to stratify for the presence of cerebral small vessel disease. Because not all participants were willing or able (due to MRI contraindications) to undergo an MRI, a sample of 220 participants underwent MRI at baseline. At four-month follow-up, half of the participants who underwent MRI at baseline underwent a second MRI to study hemodynamic aspects of the intervention.

Outline of this thesis

In Chapter two, the aim is to determine whether blood pressure level is associated with grey, white matter and subcortical brain volumes in the DANTE MRI sub-study. Then, in Chapter three, the association of blood pressure with both small vessel disease-related pathologies and cerebral microstructural integrity of the brain in the DANTE MRI sub-study is further assessed. Chapter four describes the results of the DANTE trial, in which it is studied whether a four-month discontinuation of antihypertensive treatment improves cognitive and psychological functioning in older persons with mild cognitive deficits who have been using antihypertensive medication. Chapter five is dedicated to determine whether low blood pressure is associated with low cerebral blood flow, and also examined the effect of discontinuation of antihypertensive medication on cerebral blood flow, using the DANTE MRI sub-study baseline and follow-up data. In Chapter six it is investigated whether microstructural integrity is associated with cerebral small vessel disease, and with cognitive and psychological function, in the DANTE MRI sub-study. Chapter seven provides further insight into cerebral grey matter structural covariance networks and their association with cerebral small vessel disease. It is also assessed whether these structural covariance networks are associated with cognitive function in the DANTE MRI sub-study. Finally, Chapter eight places the current findings in perspective and discusses implications for future research.
Chapter 1

References
