Chapter 1

General introduction
Blood pressure

High blood pressure (BP) is the leading risk factor for morbidity and mortality, accounting for 9.4 million deaths and 7.0% of global disability adjusted life years, particularly due to ischemic heart disease and stroke. Hypertension - defined as BP levels above 140 mmHg systolic or 90 mmHg diastolic - affects one in three adults worldwide, and the life-time risk to become hypertensive exceeds 90% in industrialized countries. The importance of hypertension as a risk factor has further been emphasized by a World Health Organization report that identified hypertension as one of the most important preventable causes of premature morbidity and mortality worldwide.

Despite the strong established risk of high BP, a growing body of evidence also suggests that a low BP, particularly diastolic BP, may increase the risk of cardiovascular morbidity and mortality. In specified patient groups such as older people, patients with coronary artery disease or diabetes mellitus, the so-called J-curve or U-curve is observed, implicating both low and high BP levels are associated with more morbidity and mortality. This might imply that lowering of BP levels beyond a certain point gives no benefit or even adverse outcomes in relation to cardiovascular morbidity and mortality.

Blood pressure and the brain

Over the last decades, hypertension has also been seen as an important contributor to dementia, including Alzheimer’s disease (AD). Mid-life hypertension in particular has been related to an increased risk of AD later in life. Suggested intermediates include vascular brain lesions such as white matter lesions (WML) and lacunar brain infarcts, and increased AD pathology such as amyloid-β plaques, hippocampal, and cortical brain atrophy. However, a J-curve has been suggested as well, with low BP levels increasing the risk for AD especially in older people. Aging, the main risk factor for AD, is associated with significant vascular changes which results in increased arterial stiffness. This may impair the cerebral autoregulation, making the brain more vulnerable for a low BP, which may predispose to cerebral hypoperfusion, in turn leading to ischemia, neuronal cell death, cognitive decline, and dementia.

Yet, it is unknown in what way blood pressure and arterial stiffness influence functioning and progression of structural brain measures. We will examine how they relate in patients with manifest arterial disease, who may be more vulnerable for early vascular aging.
Angiotensin-converting enzyme

One of the mechanisms that regulate the blood pressure is the renin-angiotensin system (RAS), with angiotensin-converting enzyme (ACE) as one of its key enzymes. The “classical” RAS is shown in Figure 1, where it is shown that renin converts angiotensinogen in angiotensin I (ANGI), and ACE in turn converts ANGI to ANGII. ANGII is a potent vasoconstrictor. Thereby, the enzymatic actions of ACE result in fluid retention and vasoconstriction, subsequently increasing the blood pressure.\textsuperscript{16}

Several RAS inhibiting antihypertensive drugs have been developed, such as ACE-inhibitors (ACEi), angiotensin II receptor type 1 blockers (ARBs), and renin-inhibitors. All these medications lead to a decline in blood pressure. Further studies continued to reveal the complexity of the RAS,\textsuperscript{16} and emerging evidence showed the presence of multiple local RAS systems, including the brain.\textsuperscript{17} It has been increasingly evident that these local RAS systems exert regulatory functions of major importance, in many cases surpassing the influence of the circulating RAS.\textsuperscript{18}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{The classic renin-angiotensin system (RAS), with a crucial role for the angiotensin-converting enzyme (ACE)}
\end{figure}
Angiotensin-converting enzyme and the brain

As a result of the discovery of a brain RAS, the role of the RAS in the etiology of Alzheimer’s disease received new levels of attention.\(^{19,20}\) However, two conflicting hypothesis exist about the relation between the RAS and risk of AD (Figure 2).

The vascular hypothesis suggests that high ACE-activity may increase the risk of Alzheimer’s disease by increasing risk of vascular brain lesions, as clinical trials showed that ACE-inhibitors reduced the risk of stroke, WMLs, cognitive decline, and dementia.\(^ {21-23}\)

The amyloid hypothesis suggests that high ACE-activity may decrease the risk of dementia by reducing accumulation of amyloid-β (Aβ). This is supported by laboratory-based studies showing that ACE degraded Aβ, and subsequent administration of ACE-inhibitors promoted the accumulation of Aβ.\(^ {24-26}\) Yet, the influences of direct measures of ACE such as serum and CSF ACE protein level and activity, in relation to the (preclinical markers of) AD have not been elucidated.

**Figure 2.** The conflicting roles of angiotensin-converting enzyme (ACE) in the etiology of Alzheimer’s disease (AD)
Thesis objectives

The first objective of this thesis was to investigate the relationship of blood pressure and arterial stiffness with brain atrophy, vascular brain lesions, and functioning in patients with manifest arterial disease.

The second objective was to investigate the relationship of the angiotensin-converting enzyme with cardiovascular events and vascular brain lesions on the one hand and brain atrophy, amyloid β accumulation, and Alzheimer's disease on the other hand.

Study populations

Data from two large cohort studies were used: 1) the Second Manifestations of ARTERial disease (SMART) study and 2) the Amsterdam Dementia Cohort of the Alzheimer Center Amsterdam.

The SMART study is an on-going prospective cohort study in patients newly referred to the University Medical Center Utrecht with manifest arterial disease or risk factors for atherosclerosis, with the aim to investigate the prevalence of concomitant arterial disease at other sites and studying the incidence of future cardiovascular events and its predictors in patients at high vascular risk. Between 2001 and 2005, patients with manifest arterial disease received an MRI of the brain in addition to standard vascular screening as part of the SMART-MR study. Follow-up measurements took place between 2006 and 2009. For this thesis, data were used from the SMART study and the SMART-MR study.

The memory-clinic based Amsterdam Dementia Cohort of the Alzheimer center of the VUmc is an on-going study that started in 2001. Patients who attend the memory-clinic receive a standardized dementia-screening including a general physical and neurological exam and medical history taking. In addition, routine laboratory tests including APOE genotyping, lumbar puncture, neuropsychological exam, EEG and MRI are performed. After the screening-day, the diagnosis is made by consensus in a multidisciplinary meeting. All patient data and biomaterial are gathered in a clinical database and accompanying biobank. The clinical research lines encompass research into the role of vascular factors in the etiology of dementia, early diagnosis and treatment of dementia, and endophenotypes for the different types of dementia.
Outline

The FIRST PART of this thesis investigates the relationship of blood pressure and arterial stiffness with brain structure and functioning in the SMART(-MR) study. In Chapter 2 we studied the relation between blood pressure measures and progression of brain atrophy during 4 years of follow-up. In Chapter 3 we investigated the relation between arterial stiffness and presence and progression of vascular brain lesions and brain atrophy during 4 years of follow-up. In Chapter 4 we examined if blood pressure and antihypertensive treatment were associated with self-rated physical and mental functioning.

In the SECOND PART of this thesis we investigated the potential conflicting relationship of ACE levels with risk of vascular disease and vascular brain lesions on the one hand, and CSF biomarkers for AD and risk of brain atrophy on the other hand. In Chapter 5 we investigated the association of serum ACE protein level and vascular risk factors with recurrent vascular events during 7 years of follow-up in the SMART study. In the SMART-MR study, we examined in Chapter 6 whether serum ACE protein level was related to progression of white matter lesions, brain atrophy and cognition during 4 years of follow-up. In Chapter 7 we examined whether serum and CSF ACE protein and activity levels were associated with the CSF AD biomarkers amyloid-β, total tau and phosphorylated tau in a memory-clinic cohort. In Chapter 8 we examined whether CSF ACE protein and activity levels in this population were associated with vascular brain lesions and brain atrophy. Chapter 9 gives a general discussion and summary of the results of this thesis.
References


