CHAPTER 9

GENERAL DISCUSSION

SUMMARY

NEDERLANDSE SAMENVATTING
Background

High blood pressure is the leading risk factor for morbidity and mortality, particularly due to ischemic heart disease and stroke. Over the last decades, hypertension has also been seen as an important contributor to dementia, including Alzheimer’s disease (AD). AD is characterized by a progressive decline in cognitive functions such as memory impairment, executive functions and language. The neuropathological characteristics are extracellular senile plaques consisting of amyloid-β (Aβ), and intracellular neurofibrillary tangles, consisting of hyperphosphorylated tau.

Epidemiological evidence showed that particularly mid-life hypertension has been related to an increased risk of AD later in life. Suggested intermediates include vascular brain lesions such as white matter lesions (WMLs) and lacunar infarcts, and increased AD pathology such as Aβ plaques, hippocampal and cortical brain atrophy. Yet, interest has been raised in the relation between low BP and adverse brain outcomes. Particularly studies in older people found that a low BP could be harmful for the brain, however other populations may also be at risk.

PART I Blood pressure and the brain

In Chapter 2 of this thesis we examined the prospective associations of baseline BP levels and change in BP levels over time with progression of global, cortical and subcortical brain atrophy in a middle-aged population with manifest arterial disease. We observed that low baseline BP levels (particularly diastolic BP levels) were associated with more progression of subcortical brain atrophy, irrespective of the course of the BP levels during the 4 years of follow-up. Next, we investigated the cross-sectional relationship between BP levels and antihypertensive drugs with self-rated mental and physical functioning (as measured by the SF-36), in patients with symptomatic and asymptomatic arterial disease (Chapter 4). We found that low baseline BP, and independently, use of antihypertensive treatment and intensity of antihypertensive treatment were associated with poorer mental and physical health status. Hence, these results suggest that the effect of BP on the brain in a high-risk population of middle-age is comparable to that of older persons in the community. This could imply that patients with manifest arterial disease are more vulnerable to early vascular aging, and have a higher biological than actual age. Several underlying mechanisms could be suggested. Possibly, a low BP
(especially low diastolic BP) in this high-risk population is an indicator of arterial stiffness. In Chapter 3 we studied the cross-sectional and prospective associations between carotid distension (as a measure of arterial stiffness) and structural brain measures in patients with manifest arterial disease. We showed that stiffening of the arteries was cross-sectionally associated with more global and cortical brain atrophy, WMLs and non-lacunar infarcts. However, arterial stiffness was not associated with changes in brain volume, WMLs and brain infarcts after 4 years. Another suggested underlying mechanism is that low BP could be an indicator of decreased cardiac output. This is in line with our observation that the association between low DBP and progression of subcortical atrophy was particularly present in patients with coronary artery disease, who may often have a lower cardiac output (Chapter 2). Finally, our population may be at increased risk of cerebral hypoperfusion through microvascular pathology and impaired cerebral autoregulation. This can make the brain more vulnerable to lower BP levels, whether resulting from antihypertensive treatment, arterial stiffness or reduced cardiac output.

Another finding in Chapter 2 was that declining systolic and diastolic BP levels over time were associated with less progression of subcortical brain atrophy only in patients with higher baseline BP levels. These results may indicate that lowering the BP is beneficial in patients with higher BP levels, but one should be cautious with further BP lowering in patients who already have a low BP.

**PART II ACE and the brain**

One of the mechanisms that regulate BP is the renin-angiotensin system (RAS). When a low BP is registered in the body this system becomes active. A key enzyme in this system is angiotensin-converting enzyme (ACE), which converts angiotensin I (ANGI) in ANGII. The latter exerts many actions in the body, all resulting in elevation of BP levels. The last decades, the role of ACE in relation to AD received increasing attention, with two hypotheses that are conflicting. The vascular hypothesis suggests that higher ACE activity leads to higher BP levels, thereby increasing the risk of vascular brain lesions and AD. Conversely, the amyloid hypothesis suggests that higher ACE activity leads to increased Aβ degradation, and hence to less plaque accumulation, decreased Aβ mediated neuronal damage and brain atrophy, and reduced risk of AD.

In Chapter 5 we examined in patients with manifest arterial disease whether serum ACE levels were associated with risk of recurrent cardiovascular events...
including vascular death, ischemic stroke and ischemic coronary heart disease (CHD). We observed that higher serum ACE levels were related to more recurrent ischemic stroke and CHD, particularly in the presence of a high blood pressure. We further investigated in this population whether serum ACE levels were associated with progression of WMLs and lacunar infarcts as measures of cerebral small-vessel disease on MRI. We found that higher serum ACE levels were borderline significantly associated with more progression of WML volume (Chapter 6). Further, we explored in a memory clinic cohort whether ACE levels and activity in cerebrospinal fluid (CSF) and serum were cross-sectionally related to cerebral small vessel disease (WMLs, lacunar infarcts and microbleeds) (Chapter 8). We showed that higher CSF and to a lesser extent serum ACE levels were borderline significantly related to more severe WMLs and presence of microbleeds, particularly in AD patients with a high blood pressure. These findings are in line with the current evidence supporting the vascular hypothesis, which mainly comes from secondary outcome measures of clinical trials showing that ACE-inhibitors reduced the risk of stroke, CSVD, cognitive decline, and dementia.

We also found support for the amyloid hypothesis. In Chapter 7 we examined the cross-sectional association between CSF and serum ACE levels and AD biomarkers in CSF (Aβ, total tau and phosphorylated tau (p-tau)). We observed that higher ACE levels, particularly in CSF, were associated with higher CSF Aβ levels, indicating less Aβ accumulation in the brain. To investigate whether higher ACE levels were also related with less brain atrophy, we examined the cross-sectional association between CSF and serum ACE levels and cortical and medial temporal lobe atrophy in a memory clinic cohort (Chapter 8). We found that higher CSF ACE levels were associated with less global cortical atrophy. Further, in patients with manifest arterial disease we related serum ACE levels with progression of global, cortical and subcortical atrophy, and we observed that higher serum ACE levels were associated with less progression of cortical brain atrophy (Chapter 5). These data suggest that ACE indeed may degrade Aβ, thereby preventing accumulation of Aβ in the brain, brain atrophy and possibly the development or rate of progression of AD. Thereby, this study is in line with the numerous laboratory-based findings (in-vitro and in animal models) showing that ACE degrades Aβ. In Chapter 9 the main findings of this thesis are described and placed in a broader context. The main conclusions are that 1) a low baseline BP was associated with more progression of subcortical brain atrophy and worse physical and mental functioning in patients with
manifest arterial disease, and a decline in BP over time was associated with less progression of brain atrophy only in patients with higher BP levels at baseline, and 2) higher ACE levels were associated with both detrimental and beneficial effect on the brain. Therefore, lowering of ACE levels, for example by ACE inhibitors, may have adverse consequences for patients with, or at risk for AD.