Hypertension, cognitive decline and dementia

Dementia is one of the most common neurological disorders in the elderly. Aging is associated with a large increase in the prevalence and incidence of degenerative (Alzheimer’s disease) and vascular dementia, leading to a devastating loss of independence. In view of increasing longevity of populations worldwide, prevention and treatment of dementia has turned into a major public health challenge. In the past decade, longitudinal studies have shown a close association between high blood pressure in middle age, cognitive decline and dementia, including Alzheimer’s disease, in the late life. Pathophysiologically, a summation of cerebrovascular damage, white matter changes and pre-existing asymptomatic Alzheimer’s brain lesions may lead to dementia, even when each type of lesion individually is not sufficiently severe to cause it. Longitudinal studies assessing the beneficial role of antihypertensive drugs on cognitive decline and dementia have produced promising results. There are few randomised placebo controlled studies, although some of these have produced positive results. Results of three recent meta-analyses are inconsistent, possibly due to methodological issues. Further long-term randomised trials, designed especially to assess a link between antihypertensive therapy and cognitive decline or dementia are therefore needed.

Résumé
Les syndromes démentiels représentent la pathologie neurologique la plus fréquente des sujets âgés. En effet, le vieillissement est associé à une augmentation importante de la prévalence et de l’incidence des démences dégénératives (Maladie d’Alzheimer) et des démences vasculaires, à l’origine d’une perte considérable d’autonomie. En raison de l’augmentation de l’espérance de vie, la prévention et le traitement de démences sont devenus un problème majeur de santé publique. Depuis les dix dernières années, plusieurs études longitudinales ont mis en évidence une association solide entre l’hypertension artérielle, mesurée en milieu de vie, et le déclin cognitif ou les démences, y compris maladie d’Alzheimer, à des âges plus avancés. Sur le plan physiopathologique, la sommation de lésions cérébrales vasculaires et de lésions dégénératives semblent contribuer à une expression anticipée d’une maladie d’Alzheimer encore infraclinique faisant atteindre le seuil de démence plus précocement. Les études observationnelles étudiant le bénéfice éventuel des traitements anti-hypertenseurs sur le déclin cognitif et la démence ont donné des résultats prometteurs. Les essais randomisés contre placebo restent peu nombreux mais certains d’entre eux mettent en évidence des

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Introduction

Because of increasing life expectancy, the number of people suffering from dementia in the world will increase from 24.3 million in 2000 to 81.1 million in 2040. Alzheimer’s disease (AD) is the main form of dementia (70% of cases) in western countries, the second leading cause (15% of cases) being vascular dementia (VaD). AD is a neurodegenerative disease associated with intraneuronal accumulation of hyperphosphorylated tau protein, forming degenerative neurofibrillary tangles and extracellular aggregation of Aβ. This aggregation results from abnormal cleavage of protein Aβ precursor (Amyloid Precursor Protein (APP)) by β- and γ-secretases, resulting in a metabolic cascade responsible for neuronal death and dementia. This major public health problem makes research into risk factors for cognitive decline and dementia a priority issue.

Many studies over the last decade have shown an association between vascular risk factors and dementia, including Alzheimer’s disease. Hypertension is a key vascular risk factor and many studies have assessed its links with cognitive decline. The aim of this article is to present the major published findings on this association and findings examining the effect of anti-hypertensive treatments on cognitive function.

Hypertension and cognitive decline

There is much and occasionally contradictory published information about the links between hypertension and cognitive function. The results depend on the methodology used, such as the type of population studied (normotensive or hypertensive), recruitment method (general population or selected sample), methods by which blood pressure were measured (several measurements, single measurement, in the outpatient clinic or ambulatory), the presence or absence of anti-hypertensive treatment, existence of other cardiovascular risk factors and cognitive function assessment method (preferentially exploring a cognitive domain or globally exploring intellectual function).

Cross-sectional studies have shown positive [1] but also negative correlations between hypertension and cognitive disorders, whereas other studies have suggested a J curve relationship between hypertension and cognitive decline. By definition, these studies are extremely heterogeneous and subject to multiple sources of methodological bias.

In this context, longitudinal studies appear to be far more informative as they assess the effect of “chronic hypertension” on cognitive function. Most of these studies show a positive relationship between midlife hypertension (around 50 years old) and cognitive decline (20-25 years later) (table 1) or dementia (Alzheimer’s or vascular) (table 2) at more advanced ages. The Framingham study [2] was one of the first to find a positive correlation between the initial blood pressure level (12 to 14 years before cognitive assessment) and cognitive decline. Later work by Kilander et al [3], in 999 men followed for 20 years showed that cognitive function assessed at the age of 70 years old was inversely related to arterial blood pressure measured at the age of 50 year old. In the EVA study [4], in older patients (average age = 65 years old) the risk of cognitive decline was 2.8 times higher (95% confidence Interval (CI)=1.6-5.0) in hypertensives after a shorter follow up period (4 years). These results have been confirmed in a far larger population (ARIC cohort; n=10,963) with a follow-up period of 6 years old [5].

Hypertension does not only increase the risk of cognitive decline but also the risk of dementia, regardless of type (vascular or Alzheimer) (table 2). The “Honolulu-Asia Aging Study” [6] found an increased risk of dementia (AD and VaD) in 50-year-old hypertensive patients after follow-up for 25 years (n=3,703). Another study which included 1,449 people showed that raised systolic blood pressure (SBP) to over 140 mmHg in midlife was associated with a significantly increased risk of AD 21 years later [7]. The “Kungsholm project” [8] suggested that pulse pressure plays a role in the elderly (81 years old) in the development of dementia. In this study, high SBP combined with a low diastolic blood pressure (DBP) were responsible for the increased risk of AD. In the same context the study found a positive association between arterial stiffness measured by the pulse wave velocity and cognitive disorders [9]. A 24% significant increase in risk of dementia 30 years later was found in hypertensive patients at inclusion in a recent retrospective study of 8,845 subjects initially between 40 and 44 years old [10]. The study by Skoog et al. [11], conducted in 1996, is particularly useful to explain the occasionally contradictory results of the different other studies. This study demonstrated that blood pressure at the age of 70 was higher in patients who developed dementia 10-15 years later than in those who did not develop dementia. Conversely, when the AD developed, a fall in

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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Alzheimer’s Disease</td>
</tr>
<tr>
<td>VaD</td>
<td>Vascular Dementia</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>95% CI</td>
<td>95% Confidence Interval</td>
</tr>
</tbody>
</table>
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Blood pressure was seen, blood pressure levels in dementia patients even becoming lower than in those who did not develop dementia. Other studies have confirmed that arterial blood pressure (BP) may be reduced in patients suffering from AD [12]. Guo et al. [13] showed that BP was lower in people over 75 years old suffering from AD than in those without dementia, and that the reduction depended on the severity of the dementia. The reasons for this fall in BP in dementia is not entirely understood: comorbidities, reduced physical activity or weight loss may contribute. In addition,

Table 1 Longitudinal studies. Association between blood pressure level and cognitive decline.

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Age at inclusion (years)</th>
<th>Follow up</th>
<th>Blood pressure threshold</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elias et al. 1993 [2]</td>
<td>1702</td>
<td>55-88</td>
<td>12-14</td>
<td>BP (continuous variable) and chronic nature of hypertension</td>
<td>Positive</td>
</tr>
<tr>
<td>Launer et al. 1995 [45]</td>
<td>3735</td>
<td>20</td>
<td>20-28</td>
<td>SBP≥160mmHg</td>
<td>Positive OR (95% CI)=2.11 (1.22-3.66)</td>
</tr>
<tr>
<td>Starr et al. 1997 [46]</td>
<td>603</td>
<td>&gt;69</td>
<td>4</td>
<td>SBP≥160mmHg</td>
<td>Positive</td>
</tr>
<tr>
<td>Kilander et al. 1998 [3]</td>
<td>99</td>
<td>50</td>
<td>20</td>
<td>DBP divided into quintiles</td>
<td>Positive</td>
</tr>
<tr>
<td>Swan et al. 1998 [47]</td>
<td>717</td>
<td>45</td>
<td>25-30</td>
<td>SBP≥140mmHg,</td>
<td>Positive Decline in memory functions and verbal learning</td>
</tr>
<tr>
<td>Tzourio et al. 1999 [4]</td>
<td>1172</td>
<td>59-71</td>
<td>4</td>
<td>SBP≥160/95mmHg</td>
<td>Positive OR (95% CI)=2.8 (1.6-5.0) OR (95% CI)=4.3 (2.1-8.8) in the absence of anti-hypertensive treatment</td>
</tr>
<tr>
<td>Knopman et al. 2001 [5]</td>
<td>10963</td>
<td>47-70</td>
<td>6</td>
<td>BP≥140/90mmHg or taking anti-hypertensive treatment</td>
<td>Positive</td>
</tr>
<tr>
<td>Reinprecht et al. 2003 [48]</td>
<td>186</td>
<td>68</td>
<td>13</td>
<td>DBP (tertiles)</td>
<td>Positive. A decline in DBP was inversely correlated with cognitive performances</td>
</tr>
<tr>
<td>Piguet et al 2003 [49]</td>
<td>377</td>
<td>≥75</td>
<td>6</td>
<td>SBP/DBP≥140/90mmHg</td>
<td>Positive</td>
</tr>
<tr>
<td>Elias et al. 2003 [50]</td>
<td>1423</td>
<td>55-88</td>
<td>4-6</td>
<td>SBP/DBP≥140/90mmHg</td>
<td>Positive only in men</td>
</tr>
<tr>
<td>Waldstein et al. 2005 [51]</td>
<td>847</td>
<td>70</td>
<td>6</td>
<td>SBP (continuous variable)</td>
<td>Positive</td>
</tr>
<tr>
<td>Kuo et al. 2005 [52]</td>
<td>2802</td>
<td>65-94</td>
<td>2</td>
<td>SBP/DBP≥140/90mmHg</td>
<td>Positive</td>
</tr>
<tr>
<td>Waldstein et al. 2008 [53]</td>
<td>1749</td>
<td>57</td>
<td>5</td>
<td>Pulse pressure</td>
<td>Positive</td>
</tr>
<tr>
<td>Guo et al. 1997 [54]</td>
<td>1736</td>
<td>75-101</td>
<td>3</td>
<td>• SBP≥180 mmHg vs 130-159 mmHg with anti-hypertensive treatment</td>
<td>J Curve OR (95% CI)=1.6 (0.9-3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• SBP&lt;130 mmHg vs 130-159 mmHg without anti-hypertensive treatment</td>
<td>J Curve - OR (95% CI)=1.9 (1.0-3.5)</td>
</tr>
<tr>
<td>Glynn et al. 1999 [55]</td>
<td>3657</td>
<td>65-102</td>
<td>9</td>
<td>SBP&lt;130mmHg or ≥160mmHg</td>
<td>J Curve</td>
</tr>
<tr>
<td>Bohannon et al. 2002 [56]</td>
<td>4136</td>
<td>65-105</td>
<td>3</td>
<td>SBP/DBP≥140/90mmHg</td>
<td>J. Curve</td>
</tr>
<tr>
<td>Tervo et al. 2004 [57]</td>
<td>747</td>
<td>60-76</td>
<td>3</td>
<td>BP≥160/95mmHg</td>
<td>Not significant</td>
</tr>
<tr>
<td>Solfirizzi et al 2004 [58]</td>
<td>1445</td>
<td>65-54</td>
<td>3.5</td>
<td>Hypertension: past history, taking anti-hypertensive treatment or BP≥140/90mmHg</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

BP = blood pressure , SBP = systolic blood pressure, DBP = diastolic blood pressure, OR (95% CI) = odds ratio (95% confidence interval)
the presence of degenerative Alzheimer’s disease lesions in the prefrontal regions causing autonomic nervous system dysfunction may contribute to the fall in BP [14].

Recent studies have also however found hypertension to have a deleterious effect on cognitive decline in overt AD. The study by Bellew et al. [15], on 700 patients suffering from AD revealed an acceleration of cognitive decline in hypertensive patients under 65 years old. This result was confirmed in a second study conducted in 135 patients suffering from AD, aged 84 years old, who were followed up for an average of 3 years [16].

In conclusion, the links between BP and cognitive function are more complex than a simple linear relationship. Chronic hypertension predisposes to cognitive decline and to the development of dementia, although a fall in BP can also been when Alzheimer’s disease develops and progresses.

### Anti-hypertensive treatments and cognitive decline

The effect of anti-hypertensive treatments on preventing cognitive decline and dementia has been assessed in observational studies and in a few randomised trials.

Results of the non-randomised trials on cognitive decline are inconsistent. The anti-hypertensive agents were initially suspected to have an adverse effect on cognitive function. Subsequently, most of the observational studies suggested that anti-hypertensive therapies had a protective effect on cognitive function. In the EVA cohort [4], the risk of cognitive decline at 4 years was significantly lower in treated, as compared to untreated hypertensives (RR (95% CI) =1.9 (0.8-4.4) versus 4.3 (2.1-8.8). Similarly, the results of a study on 1617 elderly people followed up for 5 years...
showed a 38% reduction in cognitive decline in treated hypertensives compared to untreated patients (Odds Ratio (OR) (95% CI) = 0.62 (0.45-0.84)) [17].

Other studies have prospectively evaluated the links between anti-hypertensive treatments and dementia (table 3). Three of these studies found no significant association between taking an anti-hypertensive agent and AD [18], [19], [20]. The Rotterdam study found that anti-hypertensive treatments had a role in preventing VaD although this association was not significant for AD [21]. Conversely, three other studies on large numbers of subjects found a large reduction in the risk of dementia (30% to 50% reduction) that was associated with anti-hypertensive treatment. The “Honolulu Asia Aging” study highlighted the importance of the duration of anti-hypertensive treatment: the reduction in the risk of dementia increased with each additional year of anti-hypertensive treatment [25]. Finally, a recent study suggests that anti-hypertensive treatments can also slow cognitive decline in patients suffering from AD [16].

In summary, several observational studies suggest that anti-hypertensive treatments are beneficial in preventing cognitive decline and dementia although this hypothesis can only be confirmed by data from randomised, placebo-controlled trials.

In this regard, six randomised, placebo-controlled trials on large sample sizes have been conducted. The results of these are shown in table 4. Firstly, in the MRC trial [26], in a sub-group of 2,584 patients followed up for 54 months, no difference was found in cognitive function between the treated group (Diuretics or β-blockers) and the placebo group. The relatively superficial neuropsychological assessment and short follow up period however may not have allowed a difference to be identified between the two groups.

In the SHEP trial [27], the incidence of dementia after a 5-year follow-up was not significantly different between the group which received diuretics or β-blockers (1.6%) and the placebo group (1.9%), although was slightly lower in the treated group. The interpretation of the cognitive assessments in this study may have been biased by missing neuropsychological data for many patients [28].

The vascular dementia project included in SYST- EUR trial [29] was the first to find a reduction in the incidence of dementia associated with anti-hypertensive treatments. This randomised trial included patients at 60 years old with isolated systolic hypertension. One thousand two hundred and thirty-eight patients received the active treatment which consisted of a calcium blocker (nitrendipine) which could be associated with an angiotensin converting enzyme inhibitor (enalapril) and/or a diuretic (hydrochlorothiazide), and 1,180 patients received the placebo. Sixty per cent of patients in the treatment group received the calcium blocker alone. Average follow up was limited to 2 years as the study was stopped early because of the significant benefit of the anti-hypertensive treatments in preventing cerebrovascular accidents. The incidence of dementia was significantly reduced by 50% in the treatment group compared to the placebo group (3.7 cases per 1000 patient-years in the treatment group versus 7.7 cases per 1000 patients-years in the placebo group). These results were observed for all types of dementia (VaD and AD).

At the end of the randomised, placebo-controlled phase, all patients were given the option of starting or continuing

<table>
<thead>
<tr>
<th>References</th>
<th>Number</th>
<th>Age at inclusion (Years)</th>
<th>Follow up (Years)</th>
<th>Type of dementia</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindsay et al. 2002</td>
<td>6434</td>
<td>≥65</td>
<td>5</td>
<td>AD</td>
<td>Not significant</td>
</tr>
<tr>
<td>Morris et al. 2001</td>
<td>634</td>
<td>≥65</td>
<td>4</td>
<td>AD</td>
<td>No association</td>
</tr>
<tr>
<td>Qiu et al. 2003</td>
<td>1270</td>
<td>75-101</td>
<td>6</td>
<td>AD</td>
<td>Reduction</td>
</tr>
<tr>
<td>In’t Veld et al. 2001</td>
<td>7046</td>
<td>≥55</td>
<td>2.2</td>
<td>All types of dementia</td>
<td>Reduction</td>
</tr>
<tr>
<td>Yasar et al. 2005</td>
<td>1092</td>
<td>≥60</td>
<td>11</td>
<td>AD</td>
<td>Not significant</td>
</tr>
<tr>
<td>Katchaturian et al.</td>
<td>3308</td>
<td>≥65</td>
<td>3</td>
<td>AD</td>
<td>Reduction</td>
</tr>
<tr>
<td>Guo et al. 1999</td>
<td>1810</td>
<td>≥75</td>
<td>3</td>
<td>All types of dementia</td>
<td>Reduction</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease  
RR (95% CI) = relative risk (95% confidence interval)  
VaD = vascular dementia

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**Table 3** Association between anti-hypertensives and dementia. Longitudinal studies.
anti-hypertensive treatment for 2 years (SYST-EUR 2) [30]. The incidence of dementia in the patient group which had been receiving anti-hypertensive treatment since randomisation (4 years) was compared to the patient group only taking anti-hypertensive treatment since the end of the double blind period (2 years). At 4 years there was still a difference in blood pressure between the group which initially received the anti-hypertensive treatment (n=1,485) and the group which was initially given the placebo (n=1,417). SBP was 7.0 mmHg higher and DBP 3.2 mmHg higher in the placebo group. Sixty-four patients developed dementia. Compared to the “control” group, long term anti-hypertensive treatment reduced the incidence of dementia by 55% (p=0.001) (from 7.4 to 3.3 cases per 1000 patient years). The incidence of all types of dementia was reduced (AD, VaD). After adjusting for age, sex, educational status and blood pressure at inclusion, the relative Hazard ratio associated with taking calcium blockers was 0.38 (95% CI=0.23-0.64 ; p<0.001). These results indicate that treating 1,000 patients for 5 years could avoid 20 cases of dementia (95% CI=7-33).

The principal objective of the randomised, placebo-controlled PROGRESS trial (n=6,105) [31] was to establish whether anti-hypertensive treatment (Perindopril ± Indapamide) could reduce recurrence of strokes in patients who had already suffered one. Its secondary objectives were to examine the potential effect of anti-hypertensive treatment on cognitive decline and dementia. The relative risk of cognitive decline fell by 19% (95% CI=4 to 32%) in the entire population and in 45% of patients who had recurrent strokes (95% CI=21 to 61% ; p=0.001) after 4 years’ follow up. The risk of dementia was reduced by 12% in the treatment group in the entire population (95% CI=8 to 28%) and by 34% in patients who had recurrent strokes (95% CI=3 to 55%, p=0.03). This effect was seen in both hypertensive and non-hypertensive patients. The significant reduction in the risk of dementia (by 23%; 95% CI=0 to 41%) was seen on dual therapy (SBP/DBP reduced by 12/5 mmHg) but not on monotherapy (-8%; 95% CI=-48 to 21%), when the fall in SBP/DBP was only 5/3 mmHg.

The HOPE trial [32], which included 9,297 patients suffering from vascular diseases followed up for 4.5 years showed a 41% reduction in cognitive decline associated with stroke in the angiotensin converting enzyme inhibitor group (ramipril) compared to the placebo group. The benefits were particularly apparent for cognition and language disorders. These results were found despite a relatively modest reduction in blood pressure (3.8/2.8 mmHg). The possible benefit of anti-hypertensive treatment on the development of dementia was not studied in this work.

The SCOPE trial [33] assessed the effect of an angiotensin 2 receptor antagonist ± a diuretic on cognitive function in 4,964 hypertensive elderly subjects (70-89 years old). No significant difference was found in cognitive function or dementia after a follow-up period of 3.7 years. The difference in blood pressure between the treatment group patients and placebo group patients was small in this study (3.2/1.6 mmHg). For ethical reasons, most patients in the

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>ΔSBP/DBP (Treatment - placebo)</th>
<th>Anti-hypertensive treatments</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC [26]</td>
<td>2584</td>
<td>-15.8/5 mmHg</td>
<td>- blockers or Diuretics</td>
<td>54 months</td>
<td>No significant effect on cognitive function</td>
</tr>
<tr>
<td>SHEP [27]</td>
<td>4736</td>
<td>-12/4 mmHg</td>
<td>- blockers±Diuretics</td>
<td>4.5 years</td>
<td>16% reduction in dementia</td>
</tr>
<tr>
<td>SYST-EUR [29]</td>
<td>2418</td>
<td>-8.3/3.8 mmHg</td>
<td>CCB±ACEI±Diuretics</td>
<td>2 years</td>
<td>50% reduction in dementia</td>
</tr>
<tr>
<td>SYST-EUR 2 [30](Open trial)</td>
<td>2902</td>
<td>-7/3.2 mmHg</td>
<td>CCB±ACEI±Diuretics ± others</td>
<td>4 years</td>
<td>55% reduction in dementia</td>
</tr>
<tr>
<td>PROGRESS [31]</td>
<td>6105</td>
<td>-9/4 mmHg</td>
<td>ACEI± Diuretics</td>
<td>4 years</td>
<td>19% reduction in cognitive decline (4 to 32%)</td>
</tr>
<tr>
<td>HOPE [32]</td>
<td>9297</td>
<td>-3.8/2.8 mmHg</td>
<td>ACEI</td>
<td>4.5 years</td>
<td>41% reduction in cognitive decline associated with stroke (6 to 63%)</td>
</tr>
<tr>
<td>SCOPE [33]</td>
<td>4964</td>
<td>-3.2/1.6 mmHg</td>
<td>ARA2±Diuretics</td>
<td>3.7 years</td>
<td>7% reduction in dementia (not significant)</td>
</tr>
</tbody>
</table>

CCB = calcium channel blockers
ACE I = angiotensin converting enzyme inhibitors
ARA2 = angiotensin 2 receptor antagonists
placebo group in reality were given anti-hypertensive treatment (other than candesartan). The absence of treatment benefit may be explained by this small difference in reduction in blood pressure and the relatively short follow up period. The results however highlighted the prevention of cognitive decline in patients who had already a mild cognitive impairment at inclusion (MMSE between 24 and 28), with the active treatment compared to the control group [34].

Recent meta-analyses which have included these randomised trials have provided an overview of the role of anti-hypertensive treatments on cognitive function. The 2006 Cochrane review [35] concluded that reducing blood pressure produced an 11% fall in the relative risk of developing dementia in patients without cerebrovascular abnormalities, although that this effect was not statistically significant (OR=0.89; 95% CI=0.69-1.16). This review included randomised, placebo-controlled trials lasting more than 6 months, the minimum time required to be able to observe an effect on cognitive function. Three randomised, placebo-controlled trials were included: SCOPE, SHEP and SYST-EUR, representing a total of 12,091 patients. The analysis was conducted from aggregate data and not individual patient data. In addition, the PROGRESS trial was not included in this meta-analysis, which may have contributed to the result obtained not being significant.

A second meta-analysis assessed the effect of anti-hypertensive treatments in patients suffering from cardiovascular diseases. This showed a borderline-significant trend fall (by 20%) in dementia (OR 95% CI =0.80 (0.63-1.02) [36]. The PROGRESS, SCOPE, SHEP and SYST-EUR trials were included in this meta analysis. The HOPE and MRC trial results were not included because of missing data. The failure to obtain a significant result may be explained by lack of power to detect treatment effects due to the relatively short follow up time for this type of disease. Here again, the analysis was based on studying aggregate data which are potentially less relevant than individual patient data.

The meta-analysis by Bierkenhager et al. [14] incorporated the difference in fall in blood pressure fall obtained between groups (treatment versus control) in the different trials. With a fall in SBP >5 mmHg, i.e. after excluding the SCOPE and PROGRESS-monotherapy trials, the analysis found a 25% significant reduction in dementia OR (95% CI=0.75 (0.60-0.94)). The authors stressed the potentially more important effect of the calcium blockers (SYST-EUR 1 and 2) compared to renin-angiotensin system blockers (SCOPE, PROGRESS-monotherapy).

Finally, the meta-analysis by Birns et al. [37] assessed the effect of anti-hypertensive treatments on different cognitive function. Sixteen randomised trials, i.e. 19,501 subjects were included in this meta-analysis. Eight were randomised, placebo-controlled trials and eight others compared the effect of different anti-hypertensive treatments. In 4 of these trials, the cognitive assessment was performed using the Mini Mental State Examination (MMSE), a test which assesses global cognitive function. These showed a modest but significant improvement in MMSE (Weighted Mean Difference (WMD)=0.19; 95% CI=0.19-0.19) with anti-hypertensive treatment. In five of the trials, a logic memory test was conducted. Reducing blood pressure appeared to benefit both immediate memory (WMD=0.62; 95% CI=0.21-1.02) and delayed memory (WMD=0.67; 95% CI=0.23-1.11) but not on executive functions. Anti-hypertensive treatments appear to have a heterogeneous effect on the different cognitive functions. Larger scale, randomised studies are needed to confirm these results, using precise neuropsychological tests able to assess all types of cognitive function (immediate and delayed memory, language, judgement, attention, executive functions etc.).

The results of these meta-analyses are discordant and do not allow a formal conclusion to be drawn. Additional randomised studies are needed with the primary objective of assessing the relationship between anti-hypertensive treatments and cognitive function or dementia.

**Pathophysiological mechanisms**

Several pathophysiological mechanisms may explain the association between hypertension, cognitive disorders and dementia. The histo-pathological studies show a frequent association between vascular lesions and neuropsychological lesions of AD. In 25 to 50% of cases, histological examination of dementia patients reveals the co-existence of cerebrovascular lesions and histological lesions of Alzheimer’s disease [38].

Hypertension gives rise to vascular modifications which affect blood flow and cerebral metabolism. Cognitive disorders may therefore be associated with the presence of focal ischaemic lesions (infarction, lacunae) and/or chronic ischaemia of the white matter due to small cerebral artery disease (arteriosclerosis, lipohyalinosis). It is the summation of vascular and degenerative lesions which may contribute to the early expression of still sub-clinical Alzheimer’s disease reaching the dementia threshold earlier [39] (figure 1).

**Figure 1.** Contribution of vascular lesions and degenerative lesions to clinical expression of dementia.

From Pasquier et al. [39] the additive diseases hypothesis.

Several studies have found a significant association between hypertension, the presence of white matter lesions and cognitive disorders [40]. Progression of white matter lesions has also been shown to be associated with the development of cognitive decline. A longitudinal study found an increase in risk of AD which was dependent on the volume and extent of peri ventricular white matter lesions [41]. Similarly, a very recent study has shown that white matter lesions are significantly associated with cognitive decline in patients already suffering from moderate memory disorders (Mean follow-up period=3.8±1.6 years) [42]. Interestingly, in the PROGRESS trial, anti-hypertensive
treatment reduced the progression of white matter lesions [43], suggesting a mechanism of action for this type of treatment in reducing cognitive decline.

Disorders of cerebral microcirculation and endothelial function may also be responsible for cognitive disorders in hypertensive patients. Hypertension is associated with changes in cerebral arterials and capillaries. Similarly AD is accompanied by cerebral microvascular lesions (amyloid angiopathy, adverse changes in smooth muscle and endothelial cells and in the basal membrane, hyalinosis and fibrosis) [44]. All of these vascular changes may damage the blood-brain barrier leading to increase in vascular permeability and extravasation of proteins into the cerebral parenchyma, resulting in accumulation of Aβ proteins. In addition, β-amyloid proteins can also promote excessive production of free radicals in endothelial cells, which are responsible for neuronal cell death. These factors suggest that oxidative stress may be involved in the vascular disorders and AD.

Finally, episodes of hypotension, hypoperfusion and hypoxia which are seen in hypertensive patients may contribute to the cognitive deficit in AD through a reduction in cerebral blood flow causing neuronal ischaemia in the most vulnerable regions of the brain.

Conclusion

There are solid epidemiological arguments to support an association between hypertension, particularly in midlife, and the development of cognitive disorders and dementia, including AD. Conversely, once the disease has become apparent a fall in blood pressure may be seen. The pathophysiological mechanisms underpinning this link have not yet been clearly established although the summation of cerebrovascular and degenerative lesions appears to contribute to early expression of as yet sub-clinical Alzheimer’s disease reaching the dementia threshold earlier. Longitudinal studies examining the possible benefit of anti-hypertensive treatments on cognitive decline have produced promising results. There are only a few randomised, placebo-controlled trials, some of which show positive results (SYST-EUR, PROGRESS, HOPE). The results of recent meta-analyses however remain relatively inconclusive because of the heterogeneous nature of the studies which they have included and because of methodological difficulties. Other randomised trials with the primary objective of assessing the impact of anti-hypertensive treatments on cognitive decline or dementia are therefore required, particularly in patient populations at high risk of cognitive decline (very elderly patients or patients who already have moderate cognitive disorders) and their results incorporated into new meta-analyses allowing individual data to be studied.

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References


