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Hypertension & dementia: pathophysiology & potential utility of antihypertensives in reducing disease burden.

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Abstract

Dementia is a common cause of disability and dependency among the elderly due to its progressive neurodegenerative nature. As there is currently no curative therapy, it is of major importance to identify new ways to reduce its prevalence. Hypertension is recognised as a modifiable risk factor for dementia, particularly for the two most common subtypes; vascular dementia (VaD) and Alzheimer's disease (AD). From the current literature, identified through a comprehensive literature search of PubMed and Cochrane Library, this review aims to establish the stage in adulthood when hypertension becomes a risk for cognitive decline and dementia, and whether antihypertensive treatment is effective as a preventative therapy.

Observational studies generally found hypertension in mid-life (age 45-64) to be correlated with an increased risk of cognitive decline and dementia incidence, including both VaD and AD. Hypertension manifesting in late life (age $\geq$ 65) was demonstrated to be less of a risk, to the extent that incidences of high blood pressure (BP) in the very elderly (age $\geq$ 75) may even be related to reduced incidence of dementias. Despite the evidence linking hypertension to dementia, there were conflicting findings as to whether the use of antihypertensives was beneficial for its prevention and this conflicting evidence and inconsistent results could be due to the methodological differences between the reviewed observational and randomised controlled trials. Furthermore, dihydropyridine calcium channel blockers and potassium-sparing diuretics were proposed to have neuroprotective properties in addition to BP lowering. Overall, if antihypertensives are confirmed to be beneficial by larger-scale homogenous trials with longer follow-up durations, treatment of hypertension, particularly in mid-life, could be an effective strategy to considerably lower the prevalence of dementia. Furthermore,

greater clarification of the neuroprotective properties that some antihypertensives possess will allow for better clinical practice guidance on the choice of antihypertensive class for both BP lowering and dementia prevention.

Key words: Alzheimer's disease, anti-hypertensives, dementia, hypertension, stroke, vascular dementia

Abbreviations

ATP	Adenosine trisphosphate
AD	Alzheimer's disease
ADDTC	Alzheimer's Disease Diagnostic and Treatment Centres
Aβ	Amyloid-β
ARBs	Angiotension-II receptor blockers
ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
AH	Antihypertensive
ApoE	Apolipoprotein E
ABRD	Atomic bomb radiation dose
β1-R	Beta1-adrenoceptor
BB	Beta-blocker
BBB	Blood brain barrier
BP	Blood pressure
BPLD	Blood pressure lowering drugs
BMI	Body mass index
CCBs	Calcium channel blockers
CO	Cardiac output
CVD	Cerebrovascular disease
CNS	Central nervous system
CAA	Cerebral amyloid angiopathy
CI	Confidence Intervals

CAD	Coronary artery disease
CHD	Coronary heart disease
DM	Diabetes mellitus
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised
DSM	Diagnostic and Statistical Manual of Mental State Examination
DBP	Diastolic blood pressure
FTD	Frontotemporal dementia
HR	Hazard ratio
HDLC	High-density lipoprotein cholesterol
IP3R	1,4,5-triphosphate receptor
L-VGCC	L-type voltage gated calcium channels
LBD	Lewy body dementia
LDLC	Low-density lipoprotein cholesterol
MR	Magnetic resonance
MRC	Medical research council
MMSE	Mini-mental state examination
MOCA	Montreal cognitive assessment
MI	Myocardial infarction
NDMA	N-methyl-D-aspartate
NICE	National Institute for Health and Care Excellence

NINCDS-ADRDA	National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association
NIARI-SAI	National Institute of Neurological Disorders and Stroke-Association Internationale
NINCDS-ADRDA	National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association
OR	Odds ratio
PD	Parkinson's disease
PAD	Peripheral arterial disease
PVD	Peripheral vascular disease
RCT	Randomised control trial
ROS	Reactive oxygen species
RAGE	Receptor for advanced glycation end products
RR	Relative risk
RYR	Ryanodine Receptor
SR	Sarcoplasmic reticulum.
SVD	Small vessel disease
SBP	Systolic blood pressure
TPR	Total peripheral resistance
VaD	Vascular dementia
WMHI	White matter hyperintensity.
WHO	World Health Organisation

Introduction

Dementia is a progressive neurodegenerative disease that develops most commonly in late adulthood and is predominantly characterised by cognitive decline and functional deterioration (Van Der Flier and Scheltens 2005). The symptoms of dementia vary between patients, but the associated cognitive impairment includes lack of concentration, memory loss, agnosia, apraxia, communication and speech problems, disorientation, and deterioration in executive function (Duong, Patel, and Chang 2017). The symptoms linked to dementia have detrimental impacts on the patient's health and quality of life, which only worsens as the disease advances. Cognitive decline is provoked by synaptic loss from dementia pathologies in the cerebral cortex that can trigger inflammation, glial and astrocyte activation, oxidative stress, and subsequent neurophysiological changes (Terry et al. 1991, Morrison and Baxter 2012). Many subtypes of dementia have been identified in accordance with the pathology. The most common subtypes that account for 97% of cases are Alzheimer's disease (AD; 60% of cases), vascular dementia (VaD; 20%), Lewy body dementia (LBD; 10%), frontotemporal dementia (FTD; 5%) and Parkinson's disease dementia (PD; 2%) (Duong, Patel, and Chang 2017). Clinical characteristics can vary and may be demonstrated at different time courses, based upon the brain areas affected by each subtype (**Figure 1**).

Overall, dementia affects around 47 million people worldwide (Ricci 2019). In 2021, in the UK, the total annual cost associated with dementia was estimated to amount to £25 billion (Luengo-Fernandez and Landeiro 2022). Consequently, the disease is an enormous public health, social and economic burden, that is only forecast to rise. In fact, due to the current ageing population, by 2050, 135 million people are predicted to be diagnosed

with dementia (Ricci 2019). Despite dementia being so prevalent, there is no curative drug at present, and available treatment only slows down its progression or masks the symptoms, by maintaining neuronal communication or limiting neuronal loss (Tisher and Salardini 2019). Therefore, there is an extensive unmet need for preventative therapies. Targeting modifiable risk factors may be an effective strategy for the reduction in dementia incidence. Hypertension has been recognised as a modifiable risk factor, particularly for the two most prevalent subtypes: VaD, vascular lesion aetiology, and AD, classically defined by abnormal amyloid and tau accumulation. Hypertension can lead to focal brain atrophy, increased arterial stiffness, and decreased cerebral blood flow (Jochemsen et al. 2013); therefore, hypertension may be an appropriate condition to target to potentially reduce the risk of dementia. Thus, this review explores the effect that hypertension has on cognitive decline and dementia and evaluates if blood pressure (BP) control, using antihypertensive treatment, could offer protection from subsequent dementia development.

Hypertension

According to systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements, blood pressure (BP) can be categorised into certain threshold groups as 'normal' or 'high'; the BP threshold values have been reported by the British Hypertension Society (summarised in **Table 1**). Hypertension arises when an individual has persistently elevated SBP and/or DBP as a result of increased total peripheral resistance (TPR) or cardiac output (CO) (Magder 2018). Along with dementia, hypertension is amongst the world's most prevalent and damaging age-related diseases. In fact, the World Health Organisation reported hypertension to affect approximately

1.28 billion people in 2021 (WHO 2019). Research on BP control in Scotland has found the 'rule of halves' to apply, whereby half of the population with hypertension are treated, of whom only half show efficacy to treatment (Smith et al. 1990). Many of those with hypertension are generally asymptomatic and are consequently unaware of having the condition, until the condition progresses, while some who receive treatment fail to take it. Between 20 and 60 years of age, SBP and DBP tend to rise linearly, due to the gradual increase in TPR (Franklin et al. 1997). However, from 60 years and over, the DBP typically plateaus, yet the SBP continues to rise disproportionally higher (Franklin et al. 1997). This is primarily a consequence of reduced elastin content and calcification in the vessels that can cause arterial stiffening and diminished elasticity (Pinto 2007). Therefore, vessels are less able to accommodate the systolic pulse of blood while DBP remains the same; hence, isolated systolic hypertension is common in patients over 50 years (Pinto 2007).

The most common risk factors for hypertension include ageing, diabetes, obesity, unhealthy diet, alcohol use, physical inactivity, smoking, sleep apnoea, and genetic predisposition (Chobanian et al. 2003). Hypertension increases shear stress on the vasculature walls to encourage endothelial cell dysfunction, allowing for low-density lipoprotein (LDL) cholesterol to enter and accumulate in the tunica media of the vascular smooth muscle; this can lead to lipid and foam cell aggregation producing a lipid core and atherosclerotic plaque. If this plaque becomes vulnerable, it can potentially rupture to form a thrombus that bulges into the lumen to further narrow or block the vessel, or form an embolus, whereby fragments of disrupted atheroma are transferred to distal vascular sites to block the vessel (Rafieian-Kopaei et al. 2014). Consequently, major

cardiovascular and cerebrovascular complications can occur and have serious health outcomes such as stroke, myocardial infarction, and heart failure (Frostegård 2013).

Antihypertensive treatment

Antihypertensive drugs are common therapies used to treat hypertension by reducing BP (Williams et al. 2004). According to the National Institute for Health and Care Excellence (NICE), the overall target for BP lowering is below 140/90mmHg for patients under 80 years old, and below 150/90mmHg for those 80 years old and older (NICE, 2019). There are several classes of antihypertensive agents that have distinct mechanisms of action; however, they all act to control hypertension by lowering CO, TPR, or both. The choice of therapeutic agent can vary between patients based on race, age, ethnicity, weight, and tolerance. The NICE guidelines advise that the first-line therapy to treat high BP - in addition to lifestyle changes - should be the antihypertensive classes including thiazide-like diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin-II receptor blockers (ARBs), or calcium channel blockers (CCBs) (NICE) 2019). Potassium-sparing diuretics, alpha-blockers, and beta-blockers should also be considered for prescription if further BP control is required (NICE) 2019). As hypertension affects approximately 30% of adults (Mills et al. 2016), if exposure to elevated BP is a risk for cognitive decline and dementia incidence, perhaps reducing BP may be a solution for reducing the onset of a number of cases. Of course, a great many may have undiagnosed hypertension of unknown duration who go on to develop dementia and for this group, any link cannot be made with certainty. Therefore, the primary aim of this review was to assess current literature, identified through a comprehensive literature search of PubMed (https://pubmed.ncbi.nlm.nih.gov) and Cochrane Library

(https://www.cochranelibrary.com), to determine the stage in adulthood when hypertension is a risk for cognitive decline and dementia. Further, we aimed to assess if antihypertensive drugs could be an effective preventative treatment of cognitive decline and dementia.

Neuropathological mechanisms of hypertension

The brain is highly vascularised and relies on nutrients and oxygen from the blood for energy to perform its functions. Hypertension can alter the structure and composition of the cerebral blood vessels that perfuse the brain, causing reduced blood flow and leaving the brain susceptible to hypoperfusion (Pires et al. 2013). When hypertension is persistent, defined as being present for more than 6 months, the formation of free radicals and reactive oxygen species is promoted, which encourages cell apoptosis and blood-brain barrier (BBB) breakdown (Lagrange et al. 1999; Sagar et al. 1992). When hypertension is chronic, defined as present for more than a year and requiring continued medical treatment, this can ultimately lead to neurodegeneration and cognitive impairment (Ou et al. 2020a). Hypoperfusion affects areas deep within the white matter that rely heavily on cerebral blood flow, particularly critical regions for memory processing and learning (Jackman and Iadecola 2015). Data from neuroimages indicates that chronic hypertension is associated with specific features of cognitive impairment and dementia, including large infarcts, lacunar infarcts, microinfarcts, microhaemorrhages, and white matter hyperintensities (WMHIs). Combined, these pathological features of hypertension increase the risk of cognitive decline in ageing and the risk of developing neurodegenerative disease.

Hypertension & cerebrovascular conditions

Stroke can occur as a consequence of chronic hypertension and is the primary cause of VaD (Hachinski et al., 2019; Vijayan and Reddy, 2016). Depending on the nature and origin of the stroke, cognitive decline and VaD can occur as one main event or remain subtle or even unnoticed. Due to this, there are different subtypes of VaD, including post-stroke dementia and subcortical dementia (Vijayan and Reddy, 2016). Post-stroke dementia can arise after a major stroke, or a series of small strokes, due to the blockage of an artery that instantly decreases the blood supply to the brain (Lee et al. 2018). Subcortical VaD occurs when the small cerebral vessels in the brain become diseased and is also known as small vessel disease (SVD). This is due to atherosclerotic plaque formation - predominantly driven by hypertension - that promotes the stiffening and eutrophic remodelling of the vessels (Kalaria and Erkinjuntti 2006). As a consequence, the narrowing or blockage of these vessels increases the microvascular resistance and reduces cerebral blood flow, so that the surrounding subcortical brain tissue is starved of oxygen and nutrients to make adenosine triphosphate (ATP), thus, the nerve tissue gradually becomes damaged. In addition, microhaemorrhages can be a repercussion of SVD that are also neurotoxic (Kalaria and Erkinjuntti 2006).

Vascular pathologies of Alzheimer's disease

There are two main hallmarks of AD in the brain: extracellular neurotic plaques and intracellular neurofibrillary tangles (Alonso et al., 1996; Masters et al., 2015). The pathology of AD is still extensively debated; however, current research proposes that it is triggered by the deposition of aggregated β-amyloid-42 peptides initially in the hypothalamus. This propagates the amyloid cascade, leading to the build-up of β-amyloid

plaques and neurofibrillary tangles, both of which can induce neurodegeneration in the cortex (Ricciarelli and Fedele 2017). The pathology of AD has been linked to vascular factors (Alsop, Detre, and Grossman 2000; Johnson et al. 2006).

The BBB normally functions by preventing non-selected solutes and toxic chemicals from entering the central nervous system (CNS), where sensitive neurons reside. Disruption to the tight junctions adjacent to the endothelial cells of the BBB caused by hypertension can increase the BBB permeability so that the β-amyloid peptide is able to infiltrate from the peripheral blood into the cerebral parenchyma and aggregate to form oligomers and plaques (Wang et al. 2018). Furthermore, the receptor for advanced glycation end products (RAGE) that allows β-amyloid influx from the luminal side of the BBB into the brain is upregulated on the endothelial cells of the BBB in response to hypoperfusion and ischaemia (Xing et al. 2012). Thus, β-amyloid concentrations are increased further in the brain. Moreover, RAGE expression is enhanced on vascular smooth muscle cells, pericytes, glial cells and neurons (Xing et al. 2012). RAGE has been reported to be expressed up to 60% more in the blood vessels of cerebral amyloid angiopathy (CAA) patients, suggesting that hypoperfusion encourages this (Lue et al. 2005). CAA is found in approximately 80% of AD patients and it is the deposition of β-amyloid into the tunica media of the cerebral blood vessels which can further encourage neurodegeneration (Viswanathan and Greenberg 2011).

Association between hypertension, cognitive decline & dementia

Over the last few decades, observational follow-up studies have been conducted to examine the risk hypertension poses for cognitive decline and dementia incidence over

adulthood. The duration and age at onset of hypertension appears to be a factor that influences this relationship. To recognise when BP treatment would be most effective, it is important to establish the stage of adulthood when hypertension is a risk factor for cognitive decline and dementia.

Mid-life hypertension, cognitive decline & dementia

Long-term observational follow-up trials have been conducted to establish the relationship that elevated BP in mid-life (age 45-64) has with cognitive decline and dementia onset in later decades (**Table 2 & 6**). Elevated BP in mid-life has been widely associated with a higher cognitive decline and dementia incidence in later life (Swan et al. 1998; Kivipelto et al. 2001; Yamada et al. 2003; Rönnemaa et al. 2011; Walker et al. 2019). A 15-year observational follow-up study concluded that subjects with elevated SBP during mid-life experienced a higher decline in cognitive performance and brain parenchyma, and increased WMH volume at the follow-up, in comparison to those with normal SBP in mid-life (Swan et al. 1998). The use of MRI quantification enabled a link to be made between high mid-life SBP and hallmarks of cognitive impairment. Participants with a pattern of mid-life hypertension and late-life hypotension were reported to have the highest risk for dementia, followed by those with sustained hypertension over mid-life and late-life in comparison to subjects with normal BP throughout (Walker et al. 2019). Although, the correlation between elevated mid-life SBP and higher dementia risk was demonstrated to be independent of late-life BP level (Walker et al. 2019). As Walker *et al.* (2019) included a heterogenous sample (59% women and 21% black ethnicity), these results were representative of the general American population. These studies provide evidence that mid-life hypertension is a risk for cognitive decline and dementia

incidence in later life; however, elevated SBP in mid-life occurs independently of increased dementia risk.

When investigating the risk for VaD and AD, an association has been made between mid-life hypertension and VaD incidence (Yamada et al. 2003; Ronnemaa et al. 2011). The Uppsala Longitudinal Study of Adult Men demonstrated that subjects with elevated SBP in mid-life had an increased risk for VaD up to 40 years later (Ronnemaa et al. 2011). In line with this, within a Japanese population including both males and females, the higher the SBP in mid-life, the greater was the risk of VaD in later life (Yamada et al. 2003). However, the relationship between mid-life hypertension and AD remained unclear in these populations with neither study reporting an association (Yamada et al. 2003; Ronnemaa et al. 2011). A Finnish population demonstrated a ~2-fold increased risk for AD over a 11-26 year follow-up period when diagnosed with mid-life isolated systolic hypertension in comparison to those with normal mid-life SBP (Kivipelto et al. 2001). In addition, their methodology accounted for antihypertensive use during analyses, which allowed for the robust analysis of the populations medical history, as despite treatment, a proportion of AD participants with antihypertensive treatment did not achieve target BP, which is in line with previous reports. More recently, the Framingham Heart Study, which assessed vascular risk factors and predictors for dementia across mid (age 55; 4899 participants), late (65 or 70 years old; 5511, 4588 participants, respectively) or later life (75 or 80 years old; 3496 and 2386 participants, respectively) across a 10-year period, (McGrath et al. 2022). This study reported that age-specific dementia risk scores are required; specifically at mid-life (age 55), elevated SBP and diabetes mellitus (DM) should be prioritised, while at age 65 non-stroke CVD is considered a greater risk factor. At ages

70 and 75, risk factors identified for inclusion in age-specific dementia risk were DM and stroke, while the most important factors at age 80 were DM, stroke, and antihypertensive use (McGrath et al., 2022).

The meta-analyses of 136 studies assessing the association between mid-life hypertension and dementia risk, reported that mid-life SBP >130mmHg was associated with a 34% increased risk of dementia and cognitive decline (Ou et al. 2020b) (**Table 6**). While increased DBP >90mmHg was associated with a 51% increased AD risk (Ou et al. 2020b). Further meta-analyses examined the association of AD and mid-life hypertension and found a significant association between systolic hypertension (>160mmHg) and AD (Lennon et al. 2019). However, in a minority of studies there was no significant association between diastolic hypertension and AD. These meta-analyses demonstrated that mid-life stage 1 (defined as >140/90mmHg) and stage 2 (defined as >160/95mmHg) systolic hypertension is associated with increased risk of AD, yet there was no association with diastolic hypertension. Similarly, Forte *et al.* (2020) detailed evidence of an adverse effect of high BP on cognitive performance in mid-life participants (40-64 years); yet with increasing age, this association diminished and became inconsistent. Similarly, the systematic review of 18 studies stated that there was no association between AD risk and hypertension (SBP or DBP) unless stratified for age; then there was a trend toward an adverse association between mid-life diastolic hypertension and AD (Power et al. 2011). Hence, while systematic review and meta-analyses suggest a link between mid-life hypertension and the later development of VaD, AD and cognitive impairment, there may be further potential known risk factors to consider.

Antihypertensive medication is a confounding variable in many of these studies, as shown via meta-analyses, reporting the correlation between neuroprotective mechanisms and AD risk (Levi Marpillat et al. 2013). Rönnemaa *et al.* (2011) stated that more than one third of participants were using antihypertensive medication during their study, which may have altered the relationship outcome between hypertension and dementia. It is important to note that hypertension only had a significant influence on AD development in participants with SBP ≥160mmHg (Kivipelto et al. 2001). Both Yamada *et al.* (2003) and Rönnemaa *et al.* (2011) had lower 'high BP' thresholds. This suggests that in order for mid-life hypertension to have a significant influence on AD development, there may need to be a particularly high sustained BP threshold. Combined, these studies highlight that having hypertension in mid-life increases the risk for dementia, including both VaD and AD. In summary, these studies concluded that the higher the BP, the greater the dementia incidence, particularly for AD. Thus, indicating that if BP control was introduced in mid-life, this could reduce the development of dementia in the later stages of adulthood.

Late-life hypertension, cognitive decline & dementia

The relationship between late-life (age ≥65) hypertension, cognitive decline and dementia remains less consistent (**Table 3 & 6**). Certain longitudinal studies have related late-life hypertension to an increased incidence of cognitive decline and dementia (Skoog et al. 1996; Li et al. 2007); however, others have found no association (Hebert et al. 2004; Solfrizzi et al. 2004). The Göteborg longitudinal study analysed the link between BP and dementia incidence at specific age intervals: 70-75, 75-79, and 79-85 (Skoog et al. 1996). On average, participants developing dementia in the 79-85 year age group had a

significantly higher SBP at age 70-75 years compared to those that were not diagnosed with dementia (Skoog et al. 1996). SBP was consistently higher throughout the follow-up in those that developed VaD. A higher SBP was recorded at age 70-75 years for those that developed AD; however, this correlation tended to decrease as age increased to the extent that there was an inverse relation between BP and AD risk as age increased above ~~from~~ 75 years (Skoog et al. 1996). These results support Walker *et al.* (2019), who identified subjects with mid-life hypertension and late-life hypotension as having the highest risk for dementia.

Similarly, when the risk high BP has on dementia was investigated in the age ranges 65-74, 75-84 and 85+ years at baseline, subjects in the youngest age group diagnosed with dementia had higher average SBP prior to the 8-year follow-up assessment (Li et al. 2007). However, correlating with the Göteborg longitudinal study, the dementia risk associated with high SBP declined as age increased, such that there was no correlation between SBP and overall dementia incidence in participants aged 75 years and older from baseline (Li et al. 2007). This supports the idea that the relationship between hypertension and dementia differs throughout adulthood. When AD incidence alone was investigated, no association was made between elevated BP and AD incidence at any stage of late life (Li et al. 2007). Two similar studies had shorter follow-up durations, with average participant ages being 72 and 74 at baseline and there was no significant link between late-life hypertension and cognitive impairment or dementia (Hebert et al. 2004; Solfrizzi et al. 2004). Findings from the Hisayama Study (Ninomiya et al. 2011) were supported by Li *et al.* (2007) in that there was no significant association between high BP and AD at any point in late life. However, comparable to the study by Skoog *et al.* (1996),

subjects with elevated BP in any stage of late-life were more likely to develop VaD. Notably, subjects with mid-life BP levels ≥140/90mmHg were demonstrated to have a 5-fold greater risk for VaD, regardless of late-life BP status (Ninomiya et al. 2011); this is consistent with previous findings (Walker et al. 2019).

In late-life, systematic analyses demonstrated that high SBP, low DBP and BP variability were all associated with increased dementia risk (Ou et al. 2020b). The relationship between the variability of BP and risk of cognitive decline or dementia were assessed through meta-analysis and subgroup analysis (20 studies; 7,924,168 participants) (Chiu et al. 2021). These results demonstrated that among individuals >65 years of age, highly variable SBP was associated with an increased risk of dementia, but not incidence of cognitive impairment. In later-life (>75 years), Forte *et al.* (2020) reported that the effect of high BP on cognitive performance was beneficial. Systematic analyses assessed whether hypertension is associated with increased risk of VaD (participants: 768 VaD and 9857 control; age range 57-95) (Sharp et al. 2011). Of these studies, a meta-analysis of six long-term studies indicated that hypertension was significantly related to increased risk of VaD. Further systematic reviews reported inconsistencies between studies, and that there was no clear effect of late-life hypertension on AD risk; however, meta-regression and subgroup analysis indicated that there may be variation across participant ethnicities (Ou et al. 2020b).

Based on this evidence, hypertension in the earlier stage of late life (age 65-74) is a risk factor for the overall incidence of dementia. However, when investigating subtypes, VaD was associated, but AD was not. There was no association between hypertension in the

more elderly stages of late-life (age ≥75) and the overall dementia or AD incidence, but there was with VaD. Therefore, the relationship between late-life hypertension and dementia was found to be less consistent than that in mid-life. These results suggest that lowering BP early in late life could potentially reduce the total incidence of dementia, particularly VaD, but not AD. Similarly, lowering BP in elderly late-life may only be beneficial for the prevention of VaD.

Antihypertensives & the prevention of cognitive decline & dementia

Although epidemiological and observational studies have linked hypertension to cognitive decline and dementia, there is controversy around whether antihypertensives are effective in treatment for reducing the risk. Therefore, it is important to assess observational studies and randomized controlled trials (RCTs) to establish this.

Observational studies

Observational studies are useful to evaluate the real-world applicability of evidence regarding antihypertensive use, cognitive decline, and dementia incidence. Relevant observational studies that investigate this relationship are summarised in **Table 4**. Multiple long-term observational studies have found beneficial effects from antihypertensive treatment in reducing the risk of cognitive decline and dementia (Tzourio et al. 1999; Khachaturian et al. 2006; Peila et al. 2006). The Epidemiology of Vascular Ageing Study (Tzourio et al. 1999) was a 4-year follow-up on four groups of participants: non-antihypertensive users with normal BP (control) and high BP (SBP ≥160mmHg and/or DBP ≥95mmHg), and antihypertensive users with normal BP and high BP; BP measurements and cognitive function were reassessed following baseline at

2- and 4-years. The 2-year reassessment was favourable to the study reliability as it reduced the likelihood of BP category misclassification. The authors found that the risk of cognitive decline was close to 1 for antihypertensive users with normal BP. It was higher for those with high BP using treatment, although not significantly, but those with untreated hypertension had the greatest risk for cognitive decline that was significantly higher than the control. These long-term studies indicate that antihypertensives were effective in decreasing the risk of cognitive decline in hypertensive patients, particularly when BP is lowered to a normal range. It is notable that chronically hypertensive subjects receiving antihypertensives had no heightened risk for cognitive decline after 4-years in comparison to subjects with normal BP without treatment (Tzourio et al. 1999). Furthermore, those using antihypertensives had a remarkably lower average odds ratio for cognitive decline after 4-years compared to non-antihypertensive users, despite both having similar chronic hypertensive BP measurements at baseline and 2-years. However, this outcome was limited to a small subpopulation of participants, which may account for the broad variation in outcomes (Tzourio et al. 1999). This indicates that antihypertensives may possess neuroprotective properties for the prevention of cognitive decline distinct from their ability to lower BP.

The Cache County Study (Khachaturian et al. 2006) followed antihypertensive users and non-users for 3-years and established a significant reduction in AD incidence in subjects using treatment. Users of potassium-sparing diuretics had a larger reduction in AD incidence compared to other antihypertensive classes, as the use of potassium-sparing diuretics alone significantly reduced AD risk by >70%. In addition, dihydropyridine CCBs tended to be more beneficial in comparison to non-dihydropyridines, as assessed by

hazard ratio, although this was not significant. Likewise, this trend was recognised when investigating the association between the use of dihydropyridine and non-dihydropyridine CCBs and the risk for AD (Yasar et al. 2005). Dihydropyridines tended to reduce the average relative risk for AD more than non-dihydropyridines 2- and 4-years prior to diagnosis. These observational studies did not acknowledge exposure to antihypertensive treatment prior to the initiation of the study, which could have influenced the outcome. When the association between the duration of antihypertensive medication use (<5 years, 5-12 years and 12+ years) and resulting dementia incidence was investigated, treatment was only significantly effective in reducing dementia prevalence after 12-years use or more, when compared to the untreated group (Peila et al. 2006). This suggests that the beneficial effects antihypertensives have on reducing the risk of cognitive decline and dementia are more gradual and subtle over a lengthened period of time.

In a systematic review, twelve original studies were assessed involving patients on antihypertensive agents with AD or VaD (Shah et al. 2009). These studies included antihypertensive agents, such as: CCB, diuretics or ACE inhibitors. These medications appear to be beneficial to dementia; however, only ACE inhibitors and diuretics consistently reduced the risk and progression of dementia across several studies. In further systematic analyses, the treatment of hypertension in people with dementia was assessed from 1990 onwards; this reported the prevalence of individuals with hypertension and dementia was 45%, where 73% of these individuals were on antihypertensive treatments – the most common of which were diuretics (Welsh, Gladman, and Gordon 2014). ACE inhibitors, ARBs and CCBs were more frequently

prescribed in the more recent studies included, while the use of beta-blockers and diuretics remained unchanged over time (Welsh, Gladman, and Gordon 2014). Conversely, other reports suggest the use of antihypertensives led to a 21% reduction in dementia risk, irrespective of antihypertensive class (Ou et al. 2020b).

Overall observational studies investigating whether antihypertensives are beneficial in preventing cognitive decline and dementia incidence indicate that treatment is effective. These studies also suggest that potassium-sparing diuretics and dihydropyridine CCBs may possess beneficial properties in addition to BP lowering. Despite the encouraging results from observational studies, the true effects of antihypertensives are only shown in Randomised controlled trials (RCTs).

Randomised controlled trials

RCTs are considered to generate the most reliable evidence for the efficacy of antihypertensive treatment due to trial design which minimises the influence of confounding variables on results. The relevant RCTs that have investigated the association between antihypertensive treatment and cognitive decline/dementia are summarised in **Table 5 & 6**. There were conflicting results from RCTs regarding the effectiveness of antihypertensive treatment for the reduction in cognitive decline and dementia. Only two RCTs established a significant reduction in cognitive decline and dementia incidence in the antihypertensive user group (Forette et al. 1998; 2002; Tzourio et al. 1999), while the remaining studies found no significant correlation (Applegate et al. 1994; Prince et al. 1996; Gayet and Lithell 2003; Peters et al. 2008; Anderson et al. 2011). The Systolic Hypertension in Europe I trial (SYST-EUR I) (Forette et al. 1998) was among

the initial RCTs to demonstrate a significant reduction in dementia cases in patient's responsive to antihypertensive treatment. Participants in the trial were randomly assigned to either an active treatment or a placebo, whereby 70% of those in the active group were using the CCB nitrendipine. At the 2-year follow-up, the treatment group demonstrated a 50% reduction in total dementia incidence. The trial was terminated early due to the large reduction in stroke prevalence experienced in the active group. Following this, participants were invited to continue the active treatment or placebo as an open-label trial that extended for another 1.9 years (Forette et al. 2002). Making it open-labelled implied that it was an 'unblinded' RCT, so participants were informed of having the active treatment or a placebo, and those in the placebo group were offered a switch into the active treatment group. The impact of BP lowering was shown to extend to an even larger 55% reduction in dementia incidence in the treated group in comparison to the placebo. There were 21 cases per 1000 patient years in the treated group compared to 43 in the non-treated group, which may truly reflect the benefits from antihypertensive therapy.

Despite these promising results, active treatment in the Systolic Hypertension in Elderly Program (SHEP) trial (Applegate et al. 1994) had no effect on the reduction of dementia incidence. The objective for the active treatment group in SHEP was to reduce the SBP to ≥160mmHg, whereas SYST-EUR aimed to lower SBP to ≥150mmHg. Thus, lowering BP to 160mmHg may have not been sufficient to show an obvious influential effect from treatment. One major limitation to the SHEP trial, is that due to ethical issues, open label antihypertensive treatment was provided to hypertensive participants taking the placebo. Therefore, majority of participants, including those in the placebo group, were

receiving treatment. This raises concern about the results and leaves the outcome open to question. SHEP (Applegate et al. 1994) would have been more comparable to SYST-EUR (Tzourio et al. 1999; 2003) had they used the familiar Mini-Mental State Examination (MMSE) method of cognitive screening and the Diagnostic and Statistical Manual of Mental State Examination (DSM) criteria for dementia diagnosis. Instead, the short-comprehensive assessment and referral evaluation was used, that has shown to be a competent method for the assessment of depression, dementia and disability (Gurland et al. 1984).

In accordance with this, the Medical Research Trial (Prince et al. 1996) used the paired associated learning test and the trial making test part A to assess memory and learning, respectively. Failure to provide evidence of cognitive benefit from BP lowering over 4.5 years may be attributed to the tests only evaluating two components of cognitive functioning: somatic memory and new learning. Although this covers the two domains most likely to be linked to hypertension, other factors of cognitive functioning were not assessed, so some cases of cognitive impairment may have been missed. In addition, the trial had a particularly large drop-out rate, increasing the risk of bias as the majority of dropouts were elderly and using the placebo. As SYST-EUR (Forette et al. 1998; 2002) used a more reliable neuropsychological testing and dementia diagnosis criteria, its methodology may have produced more reliable results than SHEP (Applegate et al. 1994) and the Medical Research Trial (Prince et al. 1996).

Comparable to SYST-EUR, the perindopril Protection Against Recurrent Stroke Study (PROGRESS) (Tzourio et al. 2003) and Ongoing Telmisartan Alone and in Combination

with Ramipril Global Endpoint Trial (ONTARGET) (Anderson et al. 2011) used the MMSE for cognitive screening. Both studies included participants with a history of cerebrovascular disease. ONTARGET concluded no significant difference between antihypertensive groups and their reduction in cognitive impairment. In line with SYST-EUR (Forette et al. 1998; 2002), PROGRESS (Tzourio et al. 2003) found antihypertensive users to have a considerable reduction in stroke prevalence. Treatment reduced the risk for 'all cognitive decline' significantly by 19%, however, it did not significantly reduce the risk for 'all dementia'. Interestingly, there was a significant 45% decrease in the risk for cognitive decline, and a 34% reduction in the dementia incidence in participants that experienced a stroke during the follow-up. However, no significant reduction in cognitive decline or 'other dementia' was found, when ruling out stroke-induced impairment. The average age of participants at baseline in SYST-EUR I and II was 71 years, whereas the average age in ONTARGET (Anderson et al. 2011) and PROGRESS was 66 and 64 years, respectively.

The previous studies assessed the treatment outcome for cognitive decline and dementia on subjects who were in late mid-life or early stages of late-life at baseline; however, the Hypertension in the Very Elderly Trial and Cognitive Function Assessment (HYVET-COG) (Peters et al. 2008) and the Study on Cognitive and Prognosis in the Elderly (SCOPE) (Gayet and Lithell 2003) examined the effectiveness of antihypertensives on very elderly subjects. Participants of HYVET-COG were 80 years or older while SCOPE included those from a broad range between 70-89 years at baseline. Both studies found that antihypertensive medication had no correlation with the reduction of dementia incidence; although HYVET-COG had a particularly short follow-up time due to the

beneficial effects found on stroke and mortality prevention. The benefit demonstrated from antihypertensive medication on stroke prevention, which in turn decreased the incidence of post-stroke dementia is in support of the Berlin Manifesto which believes that more than a third of dementias can be prevented by preventing stroke (Hachinski et al. 2019). As the MMSE is recognised to have low sensitivity in detecting minor cognitive impairment differences (Mitchell 2009), the duration may not be long enough to reveal the true protective effects of BP lowering on cognitive functioning. The Montreal Cognitive Assessment (MOCA) may be a preferable way for screening in short-term trials like HYVET-COG, as it is more sensitive to cognitive impairment (Mijajlovic. et al., 2017). It may also be superior to MMSE as it includes additional measurements of executive functioning, which is a known deficit in VaD. There is the ability to convert MMSE into MOCA scores, which would be appropriate to allow for a more sensitive identification of mild cognitive impairment (Wong et al. 2018). SCOPE (Gayet and Lithell 2003) used the International classification of Diseases, 10th revision criteria for dementia diagnosis to assess decline in executive functions impaired in dementia such as abstraction, judgement and problem solving. Despite the criteria being less commonly used than the standard DSM criteria, both are reported to be equally effective (Naik and Nygaard 2008). In 2009, these trials were systematically assessed, where the incidence of dementia indicated no significant difference between treatment and placebo; however, there were considerable methodological differences between trials (HYVET, SCOPE, SHEP and SYST-EUR) (McGuinness et al. 2009). In 2020, further systematic analyses were performed, where studies reported a reduction in cognitive decline (including HYVET-COG, ONTARGET, PROGRESS, and SCOPE trials) and altered cognitive impairment (including SYST-EUR, ONTARGET, PROGRESS, and SCOPE trials) (Hughes et al. 2020). Together,

antihypertensive agents were associated with a significantly reduced risk of dementia or cognitive impairment, compared to controls (12 trials: risk reduction; 7% vs 7.5% and cognitive impairment 20.2% vs 21.1%) (Hughes 2020). Similarly, meta-analyses indicated that hypertensive treatment modestly decreased cognitive decline in adults >60 years old (including SHEP, SYST-EUR, SCOPE and HYVET-COG trials) (Gupta 2020).

Current systematic reviews report no consensus on whether antihypertensive use in people with dementia may improve overall health (Beishon et al. 2014; Zonneveld et al. 2018; Rahimi et al. 2021). When systematically reviewing classes of antihypertensives, studies indicated an improvement in episodic memory in elderly patients treated with ARBs, when compared to placebo or other antihypertensive drugs (Stuhec et al. 2017). However, there was no improvement in patient cognition in those who received diuretics, beta-blockers or CCBs. Therefore, evidence suggests that ARBs are particularly useful for lowering BP and improving episodic memory in the elderly. To quantify the risk of dementia in relation to antihypertensive diuretic treatment in RCTs and observational studies, systematic review, meta-analysis and meta-regression were performed (Tully et al. 2016). Here, the authors reported that diuretics were associated with reduced dementia (15-17% reduction) and AD risk (18% reduction); in particular, potassium-sparing, thiazide and loop diuretics, yet there were insufficient data to determine the effect on VaD. Further, the meta-regression determined that demographics, cognitive function and genetic predisposition did not impact results (Tully et al. 2016). The association of classes of antihypertensive medication and the risk of dementia incidence was compared in observational studies with at least one year follow-up (469,790 participants) (den Brok et al. 2021). Meta-analyses established that CCBs or ARBs were

linked to a 12-17% ($p < 0.05$) lower risk of dementia when compared to other classes of antihypertensives, such as beta-blockers, ACE inhibitors or diuretics (7-11% lower risk; $p > 0.05$). Whether patients experienced off-target effects was not described. Therefore, this network meta-analyses concluded that CCBs or ARBs would be the first-line treatment for hypertension in individuals at risk of dementia. However, the effect antihypertensives have on cognitive decline and dementia prevention remains uncertain.

Mechanisms

Evidence has indicated that specific antihypertensive classes may have pleotropic effects, in addition to BP lowering. The dihydropyridine CCB class of antihypertensives were speculated to be particularly beneficial, especially since nitrendipine was the main active treatment used in the SYST-EUR trial (Forette et al. 1998; 2002). In support of this, a RCT and meta-analysis that compared benefits of antihypertensive classes to each other established CCBs to have the most significant benefit (Angeli et al., 2004; Van Middelaar et al., 2017). Several other studies have proposed that dihydropyridines confer neuroprotective properties (Sandin, Jasmin, and Levere 1990; Levy et al. 1991; Levere and Walker 1992; Morich et al. 1996; Mason et al. 1999). Long-term treatment with nicardipine in spontaneously hypertensive rats protected against the neurodegenerative consequences of hypertension in more ways than lowering BP (Amenta 1996). The concept of CCBs having neuroprotective properties is supported by evidence that dihydropyridines are highly lipophilic and thus can readily cross the BBB (da Costa Cabrera et al. 2019).

Calcium is important for many functions in the brain, including memory and learning. Its regulation is found to diminish in old age and under ischaemic conditions, where free

intracellular calcium levels tend to elevate (Wu and Tymianski 2018; Allen and Bayraktutan, 2009). Consequently, vasoconstriction of the cerebral blood vessels, promoted by high intracellular calcium, reduces blood flow to the surrounding brain tissue. Dihydropyridines have the ability to prevent this by encouraging vasodilation (Hanyu et al. 2007). In addition, consistently high intracellular calcium levels, induced by chronic hypoperfusion, are thought to be favourable to the cleavage of the β-amyloid protein precursor by β-secretase, to produce the β-amyloid peptide (Kawahara and Kuroda 2001). This is linked to the increased production of reactive oxygen species derived from the enzyme NADPH oxidase in response to calcium (Iadecola, Park, and Capone 2009). Calcium ions have also been shown to stimulate hyperphosphorylation of tau by the enhancement of calpain (calcium dependent protease). Active calpain induces phosphorylation of tau, favouring higher rates of tau accumulation (Cao et al. 2019). However, AD pathologies have also been found to cause calcium dysfunction. β-amyloid has shown to be responsible for the formation of cation-selective ion pores in lipid bilayers, allowing calcium to pass into the cytosol and increase intracellular concentrations (Arispe, Rojas, and Pollard 1993; Glabe 2006). Furthermore, β-amyloid may enhance calcium influx by interacting with the N-methyl-D-aspartate receptor (De Felice et al. 2007), and by causing free-radical-mediated calcium entry through L-type voltage gated calcium channels (L-VGCCs) (Ueda et al. 1997). Finally, mutations affecting tau protein that are regularly found in AD patients, alter the function of L-VGCCs and increase the voltage-dependent calcium current (Furukawa et al. 2003). Appropriately, in a rat brain, nitrendipine was shown to bind to areas of high synaptic density, particularly those affected by AD, such as the cortex, thalamus and hippocampus (Gould, Murphy, and Solomon 1985). Thus, dihydropyridines that target the L-VGCCs in the brain are

thought to have therapeutic benefits for cognitive impairment and dementia, particularly AD, as they can restrain the toxic high intracellular calcium levels. The involvement of intracellular calcium in the pathogenesis of AD and VaD and how CCBs, particularly dihydropyridines, could be protective are summarised in **Figure 2**.

Potassium-sparing diuretics were also found to have additional benefits other than BP lowering. In contrast to the mechanism of action of loop-diuretics and thiazide-like diuretics, potassium-sparing diuretics typically lead to increased potassium concentrations. Potassium supplementation and high potassium serum levels have been attributed to improved learning and reduced memory deficits in both humans and hypo-perfused rats (Ozawa et al. 2012; Zhao et al. 2013), yet the mechanism of this remains less clear. However, hypokalaemia has been linked to vasoconstriction (Chang et al. 2014), oxidative stress (Udensi and Tchounwou 2017), inflammation (Ishimitsu et al. 1996) and cell apoptosis (D'Mello et al. 1993), all of which are associated with dementia formation.

To date, no treatment exists to cure dementia, therefore it is of major importance that research investigates whether modifying risk factors is effective in preventing the disease. This review has investigated published data which has examined the risks that hypertension has for cognitive decline and dementia and the impact that antihypertensive medication could have on its prevention. One in every four adults in the western world suffer from high BP (Ashley and Niebauer 2001) and so improved BP control, particularly in mid-life, may dramatically reduce the number of dementia cases. Therefore, further efforts to clarify the relationship between antihypertensives and

dementia are of critical importance. The association established by RCTs and meta-analyses investigating the link between mid-life and early late-life hypertension and dementia suggests that more regular BP check-ups to detect and to control hypertension are warranted. Raising awareness of the risk that high BP could potentially have on cognitive impairment may also improve patient compliance to antihypertensive treatment. Identifying that dihydropyridine CCBs and potassium-sparing diuretics likely possess neuroprotective properties provides grounds for further research to evaluate this. Doing so will allow for better clinical guidance on antihypertensive choice for both BP lowering and protection against cognitive decline and dementia.

Limitations

Trials would need to overcome limitations experienced in previous studies for consistent results. There are several methodological concerns believed to be the underlying cause of inconclusive results and may explain why antihypertensives lacked benefit in some studies. Limitations of observational studies are likely to have produced inaccurate data (Tables 2 - 4). For instance, reliance on self-reporting of antihypertensive medication leaves the risk of treatment being falsely reported, especially in those experiencing early signs of memory impairments. In addition, misclassification of participant BP due to lack of BP measurements during the follow-up may have distorted results. Furthermore, drop-out and mortality rates are expected to be higher in untreated hypertensive participants. This is likely because individuals with elevated BP are at higher risk of cardiovascular and cerebrovascular disease compared to those with a controlled BP. Therefore, cognitive decline and dementia incidence in follow-up assessments attributed to hypertension may have been missed, undermining the effects of antihypertensives. Additionally, patient

compliance to drug treatment is almost impossible to measure. Failure to use treatment may have biased results towards the null hypothesis.

Despite RCTs being considered more accurate, they also have limitations (Table 5). In many studies, for ethical purposes, participants in the placebo group were offered open-label antihypertensive treatment or a switch into the active treatment group. This may have caused the BP difference between the two groups to be small, making it hard to distinguish a beneficial effect from BP lowering. Additionally, in support of the finding that hypertension in mid-life is likely to have a larger risk for dementia compared to hypertension in late-life, it is reasonable to assume that antihypertensive use in mid-life has greatest efficacy for dementia prevention. Therefore, the unexpected lack of positive outcomes from RCTs could be linked to participants included at baseline who were predominately in their latter stage of mid-life or in late-life. The RCTs were short-term, so there may have not been enough time for antihypertensives to demonstrate any preventative effects and a minimum of a 2 – 4 year follow up would strengthen the study output. As observational trials didn't include the duration of time that participants were treated for, this may explain why associations were reported. There are also various limitations to this work as there was a lack of consistency between studies. For instance, antihypertensive treatment and dosages differed, making it hard to distinguish if benefits were because of the pleotropic effects, or directly due to BP lowering. Furthermore, confounding variables that were considered during statistical analysis differed between observational studies as well as methods of neuropsychological testing. Follow-up durations varied, participant group ages were diverse, and studies had different BP reduction aims for the active treatment. Aspects including arterial stiffness and circadian

variations in BP were neglected despite being contributors to hypertension (Koroboki et al. 2012; Oh 2018). In order to address these limitations, it is essential that long-term studies which employ larger and more diverse populations, which do not rely on patient self-reporting, have consistent methodologies and analyses, adhering to the standards set by the British Hypertension Society (**Table 1**), are conducted to validate and determine the true effect of antihypertensive medication on the development of dementias.

Discussion

This review aimed to investigate the stage in adulthood when hypertension is a risk for cognitive decline and dementia. Overall, the results provided consistent evidence to support that hypertension in mid-life (age 45-64) is correlated with an increased risk for dementia in later life, including VaD and AD. Although as discussed, there are several methodological concerns believed to be the underlying cause of inconclusive results and may explain where antihypertensives lacked benefit. Hypertension in the first decade of late-life (age 65-74) was associated with an increased risk of the overall incidence of dementia, but when examining the subtype, it was a risk for VaD, but not AD. On the other hand, the overall incidence of dementia, including AD, had no relation with hypertension in elderly late-life (age ≥75), yet VaD did. We also aimed to determine if antihypertensives could be beneficial as a preventative treatment of cognitive decline and dementia. The majority of observational studies support this concept, yet RCTs and systematic reviews demonstrate inconsistent evidence, therefore results remain inconclusive.

As discovered by Swan *et al.* (1998), mid-life hypertension provokes early signs of brain ageing, including cerebral brain atrophy and WMHIs. Persistent hypertension can cause long-term irreversible damage to the vasculature by atherosclerotic plaque formation and progression. This promotes vessel wall remodelling and vascular endothelial dysfunction, that worsens over time to cause hypoperfusion and autoregulatory deficits (Deanfield, Halcox, and Rabelink 2007; Tarumi et al. 2014; Setiadi et al. 2018). Due to this, hypertension-induced neurodegeneration and cognitive impairment will develop gradually from mid-life into late-life, where other associated risk factors such as age will

also contribute to dementia development (Murman 2015). This is likely why the risk of dementia was found to be greater in subjects with hypertension throughout mid- and late-life compared to those with hypertension in late-life alone. Attempts to give treatment for hypertension to subjects in late-life with previous history of high BP may have been ineffective as they could have been exposed to elevated BP for too long to benefit from this intervention; which would indicate why antihypertensives were found to be beneficial in some patient groups when used for 12 years and over (Peila et al. 2006).

Vascular damage from hypertension in early late-life was sufficient to be a risk for the overall incidence of dementia, including VaD, but not AD. There were discrepancies among studies when taking dementia subtypes into consideration and this may be due to the difficulty in distinguishing between VaD and AD, as growing evidence has shown both pathologies to co-exist as a more recently discovered subtype termed 'mixed dementia' (Custodio et al. 2017). Epidemiological studies have found AD pathologies to be present decades before symptoms occur (Jack et al. 2010), therefore it is justifiable to consider that hypertension in mid-life can contribute to AD neuropathological changes but late-life hypertension is too late to have an influential effect. In contrast, cognitive impairment induced by stroke can be more abrupt, particularly if the stroke is major, and since stroke accounts for a large proportion of VaD cases, symptoms such as memory loss and decline in executive function are typically more sudden than AD symptoms (Venkat, Chopp, and Chen 2015). This may rationalise why late-life hypertension is still a risk for VaD but not AD. In addition, it may support why antihypertensives were found to be particularly effective in preventing dementia induced by stroke.

Individuals progressing into the more elderly stages of late-life (age ≥75) showed no correlation between hypertension and the overall dementia incidence, including AD, with certain studies demonstrating hypertension in the very elderly to be related to better cognitive scores (Nilsson et al. 2007; Mogi 2019). This is possibly due to the correlation that Walker *et al.* (2019) and other researchers have made between mid-life hypertension and late-life hypotension and dementia, implying that hypotension is a precursor to or consequence of dementia (Skoog et al. 1996; Nilsson et al. 2007; Kennelly, Lawlor, and Kenny 2009; McGrath and Seshadri 2018; Power et al. 2011; Forte and Casagrande 2020; Ou et al. 2020b; Qiu et al. 2003). The development of dementia has been correlated with a higher SBP from mid-life to late-life where BP then proceeds to fall years prior to clinical dementia diagnosis (Stewart et al. 2009). Evidence has shown that chronic hypertension can induce changes in the arterioles to cause deficiencies in the cerebral autoregulatory system, resulting in diminished baroreflex activity and dysautonomia (Burke et al. 1994). Subsequently, in AD patients, β-amyloid is known to reside in areas such as the medulla oblongata (Serrano-Pozo et al. 2011). The ventrolateral region of the medulla oblongata contains C1 neurons that are responsible for the signalling of sympathetic innervation on the heart and peripheral blood vessel to increase BP (Moretti et al. 2008). Thus, disruption and degradation of these neurons can cause low BP and ultimately lead to hypoperfusion of the brain. Increasing BP in both circumstances would increase brain perfusion. This indicates why antihypertensive use in the very elderly had no association with the decreased risk of cognitive decline and dementia incidence (Peters et al. 2008). These outcomes highlight that elevated BP in mid-life is likely the most essential period for BP control to prevent dementia.

Overall, the potential benefits that antihypertensive therapy have for dementia prevention has major public health implications which are particularly important given increased longevity in populations worldwide. Furthermore, if antihypertensive treatment is confirmed to be effective, decreasing the number of dementia cases would have significant economic and social implications, particularly by lowering the burden that dementia places on health-care systems and social services. Despite these potential implications, considerable research needs to be undertaken before any conclusions or guidance can be made. Additional evidence is required before conclusions can be drawn to whether antihypertensives are beneficial. Firstly, future trials investigating BP patterns and the risk of dementia over a lifespan are required, particularly as hypertension becomes more prevalent in the younger generation, with inaccurate screening and diagnoses. This would allow better medical guidance for when BP monitoring should start, along with treatment, and the standards set by the British Hypertension Society (Table 1). Future larger scale long-term trials that start antihypertensive regimes from early mid-life, extending into the elderly years of late-life are required to distinguish the true effectiveness of BP reduction on dementia prevention. However, there are major ethical implications regarding the use of placebos in patients with hypertension for such long durations. As well as this, RCTs can be extremely costly and perhaps not feasible for many study groups. A suggested alternative method would be longer-term studies making ethical use of previous medical records with the permission of patients, so that participants' medical histories can be followed up years before being enrolled into the study. In addition, in the future, big data repositories such as those that exist in other

disease settings, for example the virtual international stroke trials archive (Vista, n.d.), may offer an opportunity to mine large datasets retrospectively.

Future trials are also required that investigate the effect of antihypertensives on homogenous patient groups. For example, as both hypertension and dementia affect males, females and individuals of varied ethnicity differently, it needs to be considered that antihypertensive treatment could be more effective in certain subgroups of populations. Finally, gaps in published literature remain regarding the pleotropic effects that different antihypertensive classes may possess. This research found CCBs and potassium-sparing diuretics to be particularly beneficial, however previous studies have considered beta-blockers, ACE inhibitors and ARBs to have pleotropic effects (Shah et al. 2009; Johnson et al. 2012; Gelber et al. 2013; Levi Marpillat et al. 2013). Clarification of which antihypertensive class is most beneficial is essential for better clinical guidance.

Conclusions

Ageing populations of the developing world means that cognitive decline and dementia prevalence is projected to rise. There is no effective dementia treatment currently available and identifying one would have a significant beneficial impact on public health, society and the economy. Hypertension has been identified as a risk factor for dementia, thus, this review sought to establish the stage in adulthood when hypertension becomes a risk for cognitive decline and dementia, and whether antihypertensive medication would be effective as a preventative treatment. We conclude that there is an urgent need ~~his~~ for long-term homologous trials and further studies to investigate the neuroprotective properties of antihypertensives. This will clarify If antihypertensives offer protection from

subsequent development of dementia. If antihypertensive treatment is indeed beneficial, more frequent BP check-ups for early hypertensive control and antihypertensive treatment may be a viable route to reduce the incidence of dementia and the burden it entails.

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Figure Legends

Figure 1: Regions of the brain affected by dementia subtypes. The most prevalent subtypes of dementia are shown including vascular dementia (VaD; stroke-related dementia and subcortical dementia), Alzheimer's disease (AD), frontotemporal lobe dementia (FTD), Parkinson's disease dementia (PD) and Lewy body dementia (LBD). Although pathologies can spread to different areas of the brain, these are the main regions that are most commonly affected by each subtype. This figure was created with BioRender.com (2021).

Figure 2: Involvement of intracellular calcium in the pathogenesis of Alzheimer's disease (AD) and Vascular dementia (VaD), and how calcium channel blockers (CCB) are potentially protective. The left hand-side cell demonstrates the process of neuronal cell death following high levels of intracellular calcium induced by old age or ischaemia. The top right-hand side cell shows the process of vasoconstriction of the smooth muscle on cerebral blood vessels in response to high intracellular calcium. The bottom right-hand cell shows the process of neuronal cell death in an AD patient that is induced by high levels of intracellular calcium, which both encourages β-amyloid accumulation and tau hyperphosphorylation, also provoked by these pathologies. Acronyms used: Aβ, amyloid-β; AD, Alzheimer's Disease, β1-R, Beta1-adrenoceptor; BBB, blood-brain barrier; CCB, calcium channel blocker; IP3R, 1,4,5-triphosphate receptor; L-VGCC, L-type voltage-gated calcium channel; NDMA, N-methyl-D-aspartate; RYR, Ryanodine Receptor; ROS, reactive oxygen species; SR, sarcoplasmic reticulum. This figure was created on BioRender.com.

Tables

British Hypertension Society Blood Pressure Thresholds

Category	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
Normal Blood Pressure ranges:		
Optimal	<120	<80
Normal	120-129	80-84
High normal	130-139	85-89
Hypertension stages:		
Grade 1	140-159	90-99
Grade 2	160-179	100-109
Grade 3	≥180	≥110
Isolated Systolic Hypertension:		
Grade 1	140-159	<90
Grade 2	≥160	<90

Table 1: The British Hypertension Society Blood Pressure Threshold values. Systolic and diastolic blood pressure (SBP, DBP) thresholds that categorise BP measurements as normotensive or hypertensive according to the British Hypertension Society. Hypertension can be divided into grades 1, 2 or 3, depending on the BP measurements. Isolated systolic hypertension can be grade 1 or grade 2 and occurs when systolic BP is elevated but diastolic BP remains normal. This table is adapted from Williams et al. (2004).

Authors	Participants	Maximum follow-up period (years)	Measurements	Covariates	Main results
Swan *et al.* (1998)	1,029 (aged 43-59 at baseline)	15	Cognitive functioning (MMSE), cerebral brain volume and total volume of WMHIs (MR quantification)	Age, education, antihypertensive use, CVD, CHD, PAD	Higher mid-life SBP caused greater cognitive decline, larger WMHI volume and decreased brain volumes in late life
Kivipelto *et al.* (2001)	1,449 (aged 40-64 at baseline)	26	AD (DSM-IV and NINCDS-ADRDA)	Age, sex, BMI, education, MI, CVD, antihypertensive user, cholesterol lowering treatment, smoking, alcohol, diabetes mellitus, cholesterol level	Higher mid-life SBP increased risk for late-life AD (HR 2.3, 95% CI 1.0 to 5.5)
Yamada *et al.* (2003)	1,774 (aged 30-80 at baseline; midlife 30-70 years)	30	AD and VaD incidence (DSM-III-R and DSM-V)	Age, sex, smoking, alcohol, physical activity, dietary habits, BMI, diabetes mellitus, education, APOE	VaD risk increased significantly in participants with high SBP (OR 1.33, 95% CI 1.14-1.59), but risk for AD did not
Rönnemaa *et al.* (2011)	2,268 (aged 50 at baseline)	40	All-type dementia incidence (DSM-IV), VaD (NINCDS-ADRDA) and AD (ADDTC)	Age, Fasting plasma glucose, serum cholesterol, BMI, smoking, ApoE e4 carrier	High mid-life SBP associated with all-type dementia (HR 2.3, 95% CI 1.8-3.1) and VaD (HR 1.6, 95% CI 1.2-2.1), but not with AD (HR 1.0, 95% CI 0.8-1.2)
Walker *et al.* (2019)	4,761 (aged 44-66 at baseline)	24	Dementia incidence (DSM-V)	Age, sex, race, education, smoking, alcohol, BMI, total cholesterol, HDLC, LDLC, CHD history, heart failure, stroke history, diabetes, ApoE genotype, antihypertensive use	Mid-life and late-life hypertension (HR 1.49, 95% CI 1.06-2.08 per 100) and mid-life hypertension but late-life hypotension (HR 1.62, 95% CI 1.11-2.37 per 100) increased risk for dementia compared to normotensive subjects

Table 2: Observational studies investigating the association between mid-life hypertension and cognitive decline/dementia. Acronyms used: ABRD, atomic bomb radiation dose; AD, Alzheimer's disease; ADDTC, Alzheimer's Disease Diagnostic and Treatment Centres; ApoE, Apolipoprotein E; BMI, body mass index; CHD, coronary heart disease; CI, confidence Intervals; CVD, cerebrovascular disease; DSM-V, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised; HDLC, high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; MI, myocardial infarction; MMSE, Mini-Mental-State-Examination; MR, magnetic resonance; NINCDS-ADRDA, National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association; OR, odds ratio; PAD, peripheral arterial disease; SBP, systolic blood pressure; VaD, vascular dementia; WMHI, white matter hyperintensity.

Authors	Participants	Maximum follow-up period (years)	Measurements	Covariates	Main results
Skoog *et al.* (1996)	382 (aged 70 at baseline	15	Dementia incidence (DSM-III-R), AD (NINCDS-ADRDA)	Age, sex, BMI	79-85 years old dementia patients had a higher SBP at 70-75 years compared to those that did not develop dementia.
Hebert *et al.* (2004)	4,284 (aged ≥65 at baseline	6	Global cognitive function (MMSE)	Age, sex, education, stroke history, antihypertensive use, race, SBP or DBP	No significant association between SBP (p= 0.7) or DBP (p = 0.03) and change in cognitive function score
Solfrizzi *et al.* (2004)	2,963 (aged 65-84 at baseline)	3.5	Mild cognitive impairment (MMSE) and dementia (DSM-III-R)	Age, sex, education, CAD, stroke diabetes mellitus, smoking, total cholesterol, HDLC	Hypertension had no significant risk for mild cognitive impairment (RR 1.44, 95% CI 0.91-2.35) or dementia (RR 1.74, 95% CI 0.46-9.74)
Li *et al.* (2007)	2,356 (aged ≥65 at baseline)	8	Dementia (DSM-IV) and AD (NINCDS-ADRDA)	Age, sex, race (non-white/white), antihypertensive use, diabetes mellitus, CAD, CVD, ApoE4 presence, education	Higher risk for dementia in subjects aged 65-74 with high SBP (HR 1.60, 95% CI 1.07-2.35) compared to those with normal BP. High SBP at any age in late-life had no association with AD (HR 0.7, 95% CI 0.70-1.95).
Ninomiya *et al.* (2011)	668 (aged 65-79 at baseline)	17	Dementia incidence (DSM-III-R), AD (NINCDS-ADRDA) and VaD (NIND-SAI)	Age, sex, education, antihypertensive user, diabetes mellitus, kidney disease, serum cholesterol, BMI, smoking, history of stroke, alcohol	VaD incidence significantly increased with elevated BP in late-life (HR 7.26, 95% CI 1.54 to 34.17) but AD incidence did not (HR 0.67, 95% CI 0.33 to 1.37)

Table 3: Observational studies investigating the association between late-life hypertension and cognitive decline/dementia. Acronyms used: AD, Alzheimer's disease; ApoE, Apolipoprotein E; BMI, body mass index; BP, blood Pressure; CAD, coronary artery disease; CI, confidence intervals; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised; HDLC, high-density lipoprotein cholesterol; HR, hazard ratio; MMSE, Mini-Mental-State-Examination; NIARI-SAI, National Institute of Neurological Disorders and Stroke-Association Internationale; NINCDS-ADRDA, National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association; RR, relative risk; SBP, systolic blood pressure; VaD, vascular dementia.

Authors	Subjects	Maximum follow-up period (years)	Intervention	Covariates	Outcomes	Main results
Tzourio *et al.* (1999)	1,373 (aged 59-71 at baseline)	4	BB+CCB+ACEi	Age, sex, education, income, MMSE baseline, alcohol, depression, ApoE	Cognitive Decline (MMSE)	Cognitive decline was lower in antihypertensive users (RR 1.9, 95% CI 0.8-4.4) vs. non-antihypertensive users (RR 4.3, 95% CI 2.1-8.8)
Yasar *et al.* (2005)	1,092 (aged ≥60 at baseline)	11	CCB (DHP and non-DHP)	Age, gender, education, smoking, SBP, DBP, MI, heart disease history	Incidence of AD (DSM-IV and NINCDS-ADRDA)	No significant association between CCB users and AD risk (DHP-CCB RR 0.3, 95% CI 0.07-1.25 and non-DHP CCB RR 0.82, 95% CI 0.37-1.83)
Khachaturian *et al.* (2006)	3,227 (aged ≥65 at baseline)	3	ACEi, BBs, CCB and diuretics	Age, BP, education, sex, stroke history, high cholesterol history, diabetes history, MI history, ApoE	Incidence of dementia (DSM-III-R), AD (NINCDS-ADRDA)	AH medication lowered incidence of AD (HR 0.64, 95% CI 0.41-0.98), particularly potassium-sparing diuretics (HR 0.26, 95% CI 0.08-0.64)
Peila *et al.* (2006)	1,294 (aged 70-89 at baseline)	12+	AH medication	Age, BMI, BP, education, smoking, CHD history, stroke history, ApoE genotype	Dementia incidence (DSM-III-R and DSM-IV)	Risk for dementia in subjects ≥12 years treatment was lower compared to never-treated hypertensives (HR 0.40, 95% CI 0.22-0.75)

Trial	Subjects	Participant features	Maximum follow-up period (years)	Intervention	Outcomes	Main results

Table 4: Observational studies investigating the association between antihypertensive treatment and cognitive decline/dementia. Acronyms used: ACEi, angiotensin converting enzyme inhibitor; AD, Alzheimer's disease; AH, antihypertensive; ApoE, Apolipoprotein E; BB, beta-blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CHD, coronary heart disease; CI, confidence Intervals; DBP, diastolic blood pressure; DHP, dihydropyridine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised; HR, hazard ratio; MI, myocardial infarction; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association; RR, relative risk; SBP, systolic blood pressure.

SHEP (Applegate *et al.*, 1994)	4,736 (aged ≥60)	160-219 mmHg SBP and DBP <90 mmHg No history of MI or stroke	4.5	Diuretic (chlorthalidone) ± (atenolol) or a-adrenoceptor blocker (reserpine) vs. placebo	Dementia (Short-CARE test)	Non-significant 16% decrease in dementia incident
MRC Prince *et al.* (1996)	2,584 (aged 65-74)	160-209 mmHg SBP and <115 DBP	4.5	Diuretics (hydrochlorothiazide + amiloride) or BB (atenolol) vs. placebo	Cognitive performance (PALT and TMT-A)	Non-significant difference in cognitive performance test coefficients between groups; diuretics -0.31, (95% CI -0.23 to -0.39), BB -0.33 (95% CI -0.25 to -0.41), placebo -0.30 (95% CI -0.24 to -0.36)
SYST-EUR I and II (Forette *et al.*, 1998; Forette *et al.*, 2002)	SYST-EUR I and II 2,418 and 2,902, respectively (aged ≥60 at baseline)	160- 219 mmHg SBP and DBP <95 mmHg No prior history of stroke	3.9	CCB (nitrendipine)±ACEi (enalapril)±diuretic (hydrochlorothiazide) vs. placebo	Dementia (DSM-III)	SYST-EUR I - Reduced the incidence of dementia by 50% (7.7 vs. 3.8 cases per 1000 patient years; p= 0.05) SYST-EUR II- Reduced the incidence of dementia by 55% (43 vs. 21 cases per 1000 patient years; p <0.001)
SCOPE (Lithell *et al.*, 2003)	4,964 (aged 70-89 years)	160-179 SBP, and/or DBP 90-99 mmHg	3.7	ARB (candesartan)± diuretic (hydrochlorothiazide)± open-label AH	Cognitive functioning (MMSE) and dementia (ICD-10)	Non-significant decrease in cognitive functioning (113 per 1,000 in treatment vs. 125 in placebo, p>0.20) and dementia incidence (62 per 1,000 patient years in treatment group vs. 57 in placebo; p= 0.20)
PROGRESS (Tzourio *et al.*, 2003)	6,105 (mean age 64)	History of stroke or transient ischaemic attack in last 5-years	3.9	ACEi (perindopril)± diuretic (indapamide) vs. placebo	Cognitive decline (MMSE) and Dementia incidence (DSM-IV)	Reduction in cognitive decline by 19% (95% CI 4% to 32%)
HYVET-COG (Peters *et al.*, 2008)	3,336 (aged ≥80)	160-200 mmHg SBP and DBP <110 mmHg	2.2	Diuretics (indapamide)± ACEi (perindopril) vs. placebo	Cognitive decline (MMSE <24 or >3 point decline in follow-up)	Active treatment group has non-significant effect on cognitive decline compared to placebo (HR 0.85, 95% CI 0.67-1.09)
ONTARGET (Anderson *et al.*, 2011)	25,620 (aged ≥55)	CAD, PVD, or CVD, diabetes with end-organ damage	4.5	ARB (telmisartan) vs. ACEi (ramipril) vs. combination vs. placebo	Cognitive impairment (MMSE≤23)	Cognitive impairment: combination vs ramipril (OR 0.95, 95% CI; 0.85-1.07, p=0.39); telmisartan vs. ramipril (OR; 0.97, 95% CI 0.89-1.06, p=0.53), telmisartan vs. placebo (OR; 1.10, 95% CI 0.95-1.27, p=0.22)

Table 5: Randomised controlled trials investigating the association between antihypertensive treatment and cognitive decline/dementia. Acronyms used: ACEi, angiotensin converting enzyme inhibitors; AH, antihypertensive; ARB, angiotensin receptor blocker; BB, beta-blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CI; confidence intervals; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-III, Diagnostic and Statistical Manual of Mental Disorders Third Edition; HR, hazard ratio; HYVET-COG, Hypertension in the Very Elderly Trial and Cognitive Function Assessment; ICD-10,

International Statistical Classification of Diseases and Related Health Problems tenth edition; MI, myocardial infarction; MMSE, Mini-Mental State Examination; MRC, Medical Research Council; OR, odds ratio; ONTARGET, Ongoing Telmisartan and in Combination with Ramipril Global Endpoint Trial; PALT, paired associated learning test; PROGRESS, the Perindopril Protection Against Recurrent Stroke Study; PVD, peripheral vascular disease; SBP, systolic blood pressure; SCOPE, Study of Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; Short-CARE; the short- comprehensive assessment and referral evaluation; SYST-EUR; systolic hypertension in Europe; TMT-A, trail making test part A..

Authors	Studies reviewed	Midlife hypertension	Late-life hypertension	Antihypertensive treatment
Shah *et al.* (2009)	12 studies for systematic review; AD & VaD patients on AH agents.	n/a	n/a	12 studies; ACEi and diuretics reduced the risk of dementia progression.
Sharp *et al.* (2011)	11 studies for systematic review of VaD & hypertension; 6 taken for meta-analysis.	n/a	11 studies (768 VaD & 9857 control cases); meta-analysis indicated a significant association between hypertension and VaD prevalence in later life (60-88 years).	n/a
McGuinness *et al.* (2010)	Four studies for systematic review; 15,936 patients; later-life AH treatment.	n/a	Average age of patients was 75.4 years across studies.	No significant difference between treatment & placebo.
Power *et al.* (2011)	18 studies for systematic review.	Suggestion of adverse association between hypertension and AD in midlife (<65 years), when adjusted for age.	Suggestion of inverse association between hypertension and AD in late-life (>65 years).	n/a
Welsh *et al.* (2014)	13 studies for systematic review; AH treatment & dementia	n/a	Average age of patients across studies was 82 years.	Hypertension prevalence 45% in dementia cases; 73% of which prescribed AH (ACEi, ARBs or CCBs, most commonly).
Beishon *et al.* (2014)	Systematic review: 6 studies; hypertension in late-life dementia	n/a	Four RCTs; mild-to-moderate dementia; no clear evidence of effect on cognition, physical function, or cardiovascular health.	Two studies compared AH; no clear consensus, but evidence suggests BP lowering in mild-moderate dementia.
Tully *et al.* (2016)	15 studies for systematic review, meta-analysis, meta-regression; 52,599 participants.	n/a	n/a	Reduced dementia & AD risk after treatment with potassium sparing, thiazide & loop diuretics. Insufficient data for VaD.
Zonneveld *et al.* (2018)	11 studies for systematic analysis; 385, 742; BPLDs vs placebo in patients with stroke & dementia.	n/a	n/a	Reduced recurrent stroke in participants with ACEi or diuretic treatment. No subgroup analysis by age performed.
Lennon *et al.* (2019)	7 studies for systematic review; SBP & AD association.	4 studies; systolic hypertension >140 & >160mmHg associated with AD risk; no association for diastolic hypertension.	n/a	n/a

Forte *et al.* (2020)	68 studies; 154, 935 participants. High BP on cognitive performance in aging.	High BP linked to poorer cognition in mid-life (40-64 years); association lessened with age.	Later-life (>75 years) & high BP association was non-linear, suggesting a beneficial for cognitive performance.	n/a
Hughes *et al.* (2020)	14 RCTs for systematic review; 96,158 patients. 12 studies for meta-analysis. AT & cognition.	n/a	n/a	8 studies reported a reduction in cognitive decline & 8 studies reported altered cognition; AT associated with reduced risk of dementia & cognitive impairment significantly.
Ou *et al.* (2020)	209 studies; 73 for systematic review. 139 for meta-analyses.	1.19- to 1.55-fold risk of cognitive disorders; >130mmHg SBP associated with 34% increased risk of dementia; >90mmHg DBP with 51% increased AD risk.	High SBP, low DBP, excessive BP variation & orthostatic hypotension associated with increased risk. Meta-regression indicated the association may vary with comorbidity ($p > 0.05$).	Treatment resulted in 21% reduction; protective window between 90-100mmHg BP to lower risk.
Stuhec et al. (2020)	Systematic review; 15 studies; classes of AT in dementia.	n/a	Improvement in episodic memory in elderly patients treated with ARBs, compared to placebo.	No improvement in cognition in patients treated with diuretics, beta-blockers or CCBs.
Gupta *et al.* (2020)	Meta-analysis 9 RCTs; 34, 994 patients; AH treatment & cognitive decline.		Adults >60 years old; modest decrease in cognitive decline.	Unable to evaluate due to limited studies with single class of antihypertensive.
Den Brok *et al.* (2021)	Systematic review & meta-analysis; 15 observational studies & 7 RCTs; 649, 790 participants.	n/a	n/a	Insufficient RCTs for analysis. Meta-analysis of observational studies reported CCBs or ARBs linked to lower risk of dementia.
Rahimi *et al.* (2021)	Meta-analysis of 5 RCTs, antihypertensives in AD patients.	n/a	n/a	AT improved cognition & behavioural AD symptoms.
Chui *et al.* (2021)	Meta-analysis & subgroup review; 20 studies	>65 years of age variable SBP associated with increased dementia risk, not cognitive decline.	n/a	n/a

Table 6: Systematic review & meta-analyses investigating the association between antihypertensive treatment and cognitive decline/dementia across mid-life and/or later life. Acronyms used: ACEi, angiotensin converting enzyme inhibitor; AD, Alzheimer's disease; AH, antihypertensive; ARB, angiotensin II receptor blocker; BP, blood pressure; BPLD, blood pressure lowering drugs; CCB, calcium channel blocker; DBP, diastolic blood pressure; RCT, randomised control trial; SBP, systolic blood pressure; VaD, vascular dementia.

21st September 2023

Professor Michael Curtis
Editor in Chief
Pharmacology & Therapeutics

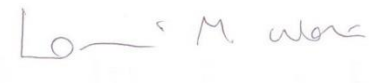
Dear Professor Curtis

Proposal No. PANDT-D-21-00275

Please find enclosed our manuscript **"*Hypertension and dementia: Pathophysiology & potential utility of anti-hypertensives in reducing disease burden*"**.

The author(s) declare no potential conflicts or competing interests with respect to the research, authorship, and/or publication of this article.

Yours sincerely



(on behalf of all the authors)

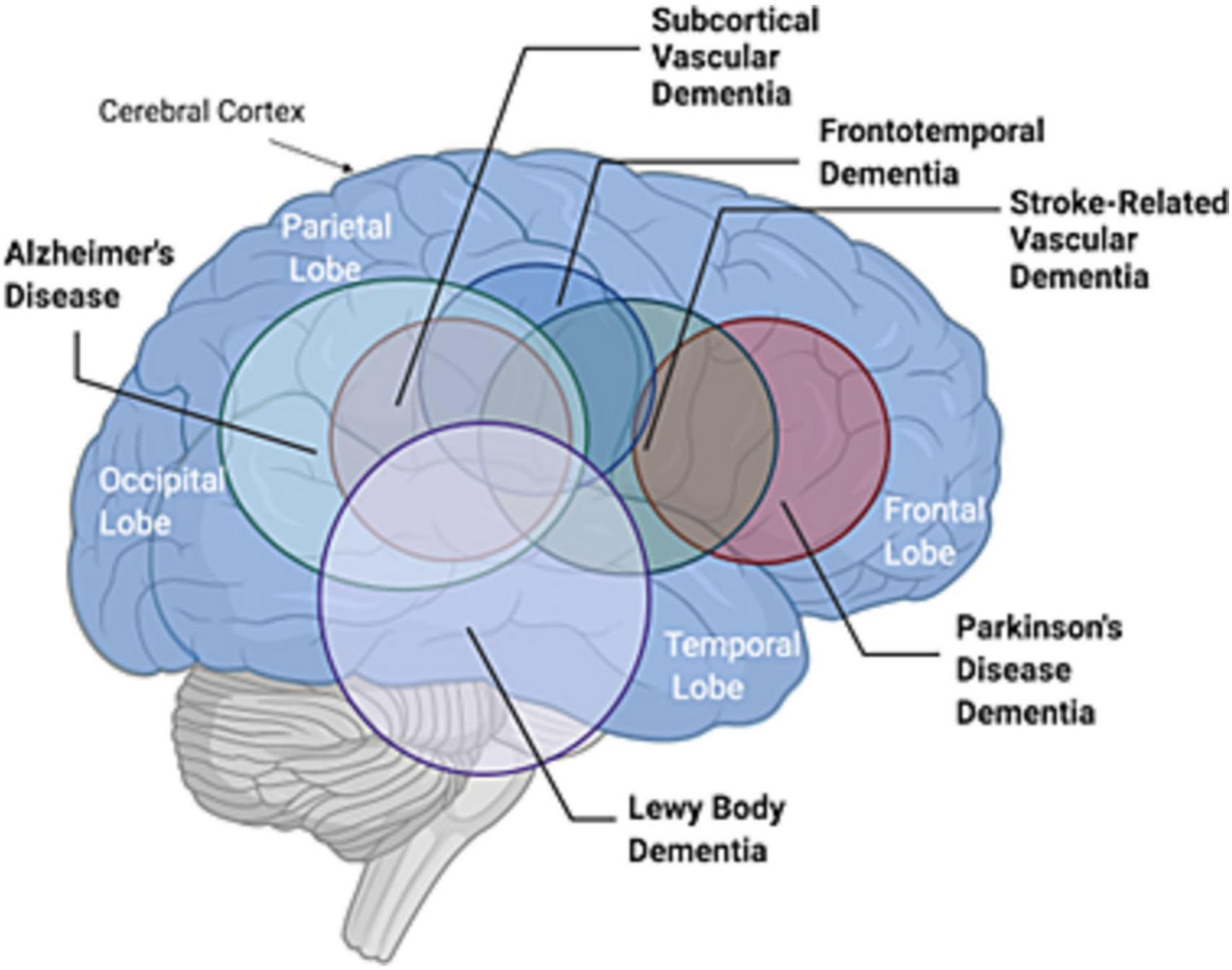

Subcortical Vascular Dementia
Cerebral Cortex
Frontotemporal Dementia
Stroke-Related Vascular Dementia
Parietal Lobe
Alzheimer's Disease
Occipital Lobe
Frontal Lobe
Temporal Lobe
Parkinson's Disease Dementia
Lewy Body Dementia

Figure 1

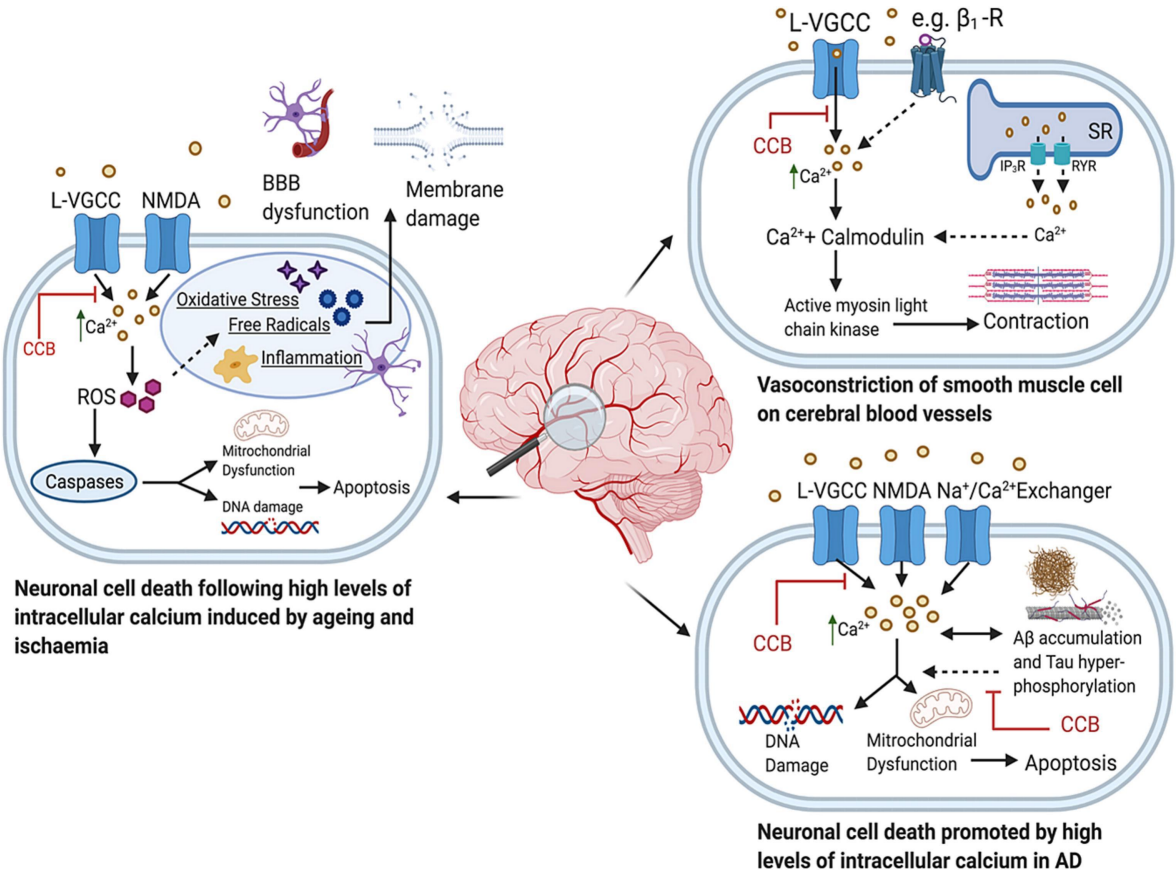

L-VGCC
NMDA
BBB dysfunction
Membrane damage
Oxidative Stress
Free Radicals
Inflammation
CCB
Ca2+
ROS
Caspases
Mitrochondrial Dysfunction
Apoptosis
DNA damage
Neuronal cell death following high levels of intracellular calcium induced by ageing and ischaemia
L-VGCC
e.g. β1-R
CCB
Ca2+
SR
IP3R
RYR
Ca2+ + Calmodulin
Ca2+
Active myosin light chain kinase
Contraction
Vasoconstriction of smooth muscle cell on cerebral blood vessels
L-VGCC NMDA Na+/Ca2+Exchanger
CCB
Ca2+
Aβ accumulation and Tau hyper-phosphorylation
CCB
DNA Damage
Mitrochondrial Dysfunction
Apoptosis
Neuronal cell death promoted by high levels of intracellular calcium in AD

Figure 2