Commentary

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Antihypertensives in dementia: Good or bad for the brain?

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Abstract

We discuss the current evidence for both benefit and harm of antihypertensive treatment in people with dementia. We conclude that there is a lack of evidence to support the claim that there is an increased risk of cerebral hypoperfusion with antihypertensive treatment in dementia, and that there is growing evidence which refutes this claim.

Keywords

Cerebral autoregulation, dementia, hypertension, orthostatic hypotension, side effects

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Should we treat high blood pressure in people with dementia with antihypertensives? To answer this question, we must weigh the benefits and risks of antihypertensive treatment in this population. In the absence of clinical trial evidence, we pose that the benefits and risks of treatment in people with dementia do not markedly differ from those in healthy peers. The majority (>80%) of people with dementia are relatively old (age >75 years), and have a high prevalence of cardiovascular comorbidity, including hypertension (~50%).[1] There is a reduced risk of cardiovascular disease or mortality associated with antihypertensive treatment (Supplementary reference [SR] #1), even in people aged >80 years (SR #2), many of whom may be at risk of dementia. Moreover, intensive treatment (i.e. systolic blood pressure target <140 mmHg) is superior to a more conservative approach, provided that the life expectancy at the onset of treatment is ≥3 years.[2] However, this is based on trials in healthy older individuals, which questions the applicability in vulnerable patient groups, e.g. patients with dementia (SR #3).

Life expectancy is shortened by dementia, but on average patients live for another 4.1 years after their diagnosis, and a healthier lifestyle may increase this number (SR #4,5). Given that hypertension contributes to the most common types of dementia, i.e. Alzheimer's disease and vascular dementia, and supported by recent clinical trial evidence, antihypertensive treatment may be helpful in the prevention and treatment of Alzheimer's disease and vascular dementia through its effects on microvascular disease progression.[3,4] More importantly, reducing the risk of stroke, myocardial infarction, heart failure or other cardiovascular events in people with dementia can help to maintain quality of life and prevent stepwise event-related deterioration of dementia. On the other hand, lifetime extension by antihypertensive treatment contributes to polypharmacy

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and may lead someone to develop more advanced stages of dementia.

Are people with dementia at increased risk of harm due to antihypertensive treatment? The assumption behind that question is that these patients have a higher risk of developing cerebral hypoperfusion when treated with antihypertensives (SR #3). The evidence for this is weak or absent. Indeed, patients with dementia show lower baseline levels[5] and faster reduction rates[6] over time in cerebral blood flow, when compared to healthy peers. However, there is no evidence for an impairment in static or dynamic cerebral autoregulation, which have both been thoroughly investigated in ageing, hypertension, and dementia due to Alzheimer's disease (SR #6).[1] Most importantly, reductions in blood pressure by antihypertensive treatment are not accompanied by decreased cerebral blood flow, and may even increase cerebral blood flow (SR #7).[1,7,8] There is thus no longer a rationale to support the notion that older people with dementia require higher blood pressure levels to maintain cerebral blood flow.[1] Furthermore, a recent meta-analysis found no evidence for a fixed 'rightward shift' of the autoregulation curve due to hypertension, that would lead to hypoperfusion when blood pressure is reduced.[7] All this may seem at odds with the widespread cerebrovascular pathology that often accompanies dementia: small vessel disease, amyloid angiopathy, blood-brain barrier dysfunction, reduced carbon dioxide reactivity, and impaired neurovascular coupling.[5] Added to this are the reductions in cerebral blood flow, together with increases in cerebrovascular resistance which, at least in Alzheimer's disease, are already observed in the early stages of disease (SR #8,9).[6] However, intact autoregulation has been confirmed in both early and late stages of Alzheimer's disease, in patients with reduced carbon dioxide reactivity and with MRI evidence of small vessel disease (SR #6).[1,5,8] Intensive blood pressure lowering in hypertensive patients without dementia but with extensive small vessel disease, or with MRI atrophy patterns suggestive of Alzheimer's disease, did not lead to reductions in cerebral blood flow.[1]

Impaired carbon dioxide reactivity could indicate a limited capacity for vasodilation, which could predispose to hypoperfusion in a context of antihypertensive blood pressure reduction. However, antihypertensive treatment does not affect carbon dioxide reactivity (SR #10), and impaired carbon dioxide reactivity does not translate to an impaired autoregulatory vasodilator response and subsequent reductions in cerebral perfusion with antihypertensive treatment (SR#10).[1,5]

Hypertension can cause impaired neurovascular coupling, thus inadequate increases in cerebral blood flow in response to neural activity required for a cognitive (or other) task. Hence treating hypertension may theoretically prevent or even restore impairments in neurovascular coupling.[1] While global cerebral hypoperfusion could negatively affect the regional flow increase in neurovascular coupling, it does not automatically follow that antihypertensive blood pressure lowering would impair neurovascular coupling. For example, adults with controlled hypertension and age-matched normotensive controls demonstrate similar neurovascular coupling (SR #11).

Recent trials have compared intensive blood pressure lowering to more conservative treatment in older hypertensive patients, some of whom developed cognitive impairment or dementia over the course of the trial.[1,9] This means that some participants had undiagnosed or preclinical Alzheimer at baseline. If intensive blood pressure lowering would cause cerebral hypoperfusion due to impairments in carbon dioxide reactivity, neurovascular coupling, or (for those still unconvinced) autoregulation, we would have seen more pronounced cognitive impairment or dementia development in the intensive group compared to the conservative treatment group. However, the reverse was true.[1,9]

Another proposed mechanism for antihypertensive treatment to cause cerebral hypoperfusion is orthostatic hypotension (OH), where the hypothesis is that antihypertensives increase the risk of OH. There is ample reason for confusion. Neurogenic OH is caused by autonomic dysfunction, and is associated with specific but rare causes of dementia (e.g. Parkinson, Lewy body)[1] but not with other dementias such as Alzheimer's disease (SR #12).[8] While neurogenic OH can be aggravated by antihypertensive medication, the most common form of OH in older patients is not neurogenic, i.e. not caused by autonomic dysfunction, but is associated with hypertension and cardiovascular disease (SR #13).[10] The association between OH and increased risk of dementia is explained by the fact that hypertension and cardiovascular diseases increase the risk of having OH, as well as the risk of dementia.[1] Recent trials have found no increase in OH with intensive versus conservative antihypertensive treatment in older patients without dementia.[10] In mild to moderate Alzheimer's disease, a low dose calcium channel blocker, compared to placebo, did not increase OH (SR #12).[8] Deprescribing antihypertensive medication in people with hypertension and OH led to worsening of OH (SR #13). Finally, a recent deprescribing trial of antihypertensives in nursing home patients was stopped because of adverse events in the stop group (SR #14).

In conclusion, we believe that it is the suggested risks, rather than the suggested benefits for antihypertensive treatment in dementia that lack evidence, as summarized in Supplementary Table S1. Decisions around treatment in patients with dementia should always be personalised, and take into account benefits,

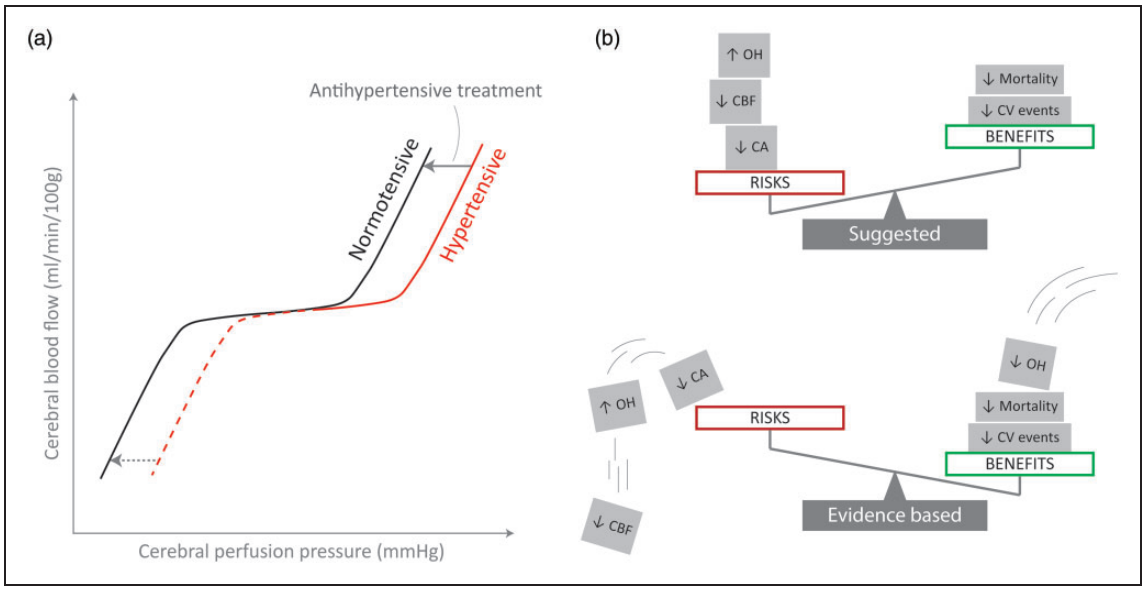

Figure 1. Postulated versus evidence based benefits and risks of antihypertensive treatment in people with dementia. (a) Cerebral autoregulation curve demonstrating the relationship between cerebral blood flow and cerebral perfusion pressure. The rightward shift in cerebral autoregulation caused by hypertension can be restored to the normotensive curve by antihypertensive treatment. Whether or not there are shifts of the cerebral autoregulation due to hypertension and/or subsequent antihypertensive control is less understood for the lower curve limit, indicated by the dashed lines and (b) Theoretical balances demonstrating how benefits and risks are often perceived (upper balance) and how we interpret them based on the available evidence (lower balance). It has often been suggested that the risks of antihypertensive treatment in dementia may outweigh its benefits, but the available evidence points towards the opposite.

risks, comorbidity, life expectancy and patient preference. Importantly, we propose that clinicians start this personalised decision making based on a correct interpretation of benefits and risks, and to consider an intensive (systolic blood pressure target <140 mmHg) rather than a more conservative approach (e.g. systolic blood pressure target >150 mmHg), as recently argued for frail older adults, including patients with dementia (SR #15,16). Based on the available evidence, we show that the benefits generally outweigh the risks of antihypertensives in dementia (Figure 1).

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Supplementary material

Supplemental material for this article is available online.

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