HHS Public Access

Author manuscript

*Hypertension*. Author manuscript; available in PMC 2023 October 01.

Published in final edited form as:

*Hypertension*. 2022 October ; 79(10): 2170–2172. doi:10.1161/HYPERTENSIONAHA.122.19859.

# Angiotensin receptor blockers and Dementia Prevention: Don't RAS to a Conclusion yet

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In this issue of *Hypertension*®, Deng et al. [1] investigate the longitudinal effect of antihypertensive medications acting via the renin-angiotensin system. They examine the effects of both angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin 1 receptor blockers (AT1RB) in participants with hypertension and mild cognitive impairment on all-cause dementia risk and cognitive function. The authors used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. They included 403 participants aged 74 years with a history of hypertension (defined as reported hypertension, reported use of AHM use, or systolic blood pressure ≥ 140 mmHg and diastolic blood pressure DBP ≥ 90 mmHg) and having a diagnosis of mild cognitive impairment (at baseline visit or follow-up). The cohort was followed for approximately 3 years. The authors report that participants using AT1RB had a significantly lower annual risk, 55%, 51%, and 69%, of developing dementia compared to participants using ACE-I, other- or no-antihypertensive users. In contrast, ACE-I or other-antihypertensive medication users did not show dementia risk reduction. The authors found a beneficial effect of AT1RB use over time on slowing the progression of a clinical dementia rating severity measure and verbal memory.

Dementia is a rapidly growing clinical and public health issue, primarily due to the increasing number of older people.[2] Mild cognitive impairment is defined as having cognitive and objective deficits on tests with preserved functional independence.[3] People with mild cognitive impairment are at ~30% greater risk of developing dementia over 3 years.[3] There is currently no effective treatment to prevent progression from mild cognitive impairment to dementia or to treat dementia.

Hypertension, especially in mid-life, is associated with increased risk for both vascular dementia and Alzheimer's disease.[4,5] These findings have resulted in an increased interest in treating hypertension as a means to reduce dementia risk, and more recently, a handful of trials are examing antihypertensive medications acting through the renin angiotensin system for reducing Alzheimer's disease risk and progression. Several observational and big data studies have shown a beneficial effect of AT1RB medications on dementia risk reduction.[7] Despite these positive results, two recent meta-analyses found no evidence that any particular antihypertensive medication class was more effective in dementia risk

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reduction compared to other- or no-antihypertensive medication use.[8,9] Yet, it is important to note that most observational studies included participants with normal cognition at baseline, had a short follow-up, and only one studied mid-life exposure. Moreover, the ability of certain antihypertensive medications acting through the renin angiotensin system to cross the blood-brain barrier has been identified as key to the potential brain-related benefits, and few studies, including this study, account for this factor.

Despite the extensive literature, there are still many unanswered questions. Few studies have evaluated the effect of antihypertensive medications on progression from mild cognitive impairment to dementia, and Deng et al. are one of the few who try to fill this gap. This study is unique since it is the only study in AT1RBs to include Alzheimer's disease cerebrospinal fluid biomarkers in participants with mild cognitive impairment.

However, like with all pharmacoepidemiologic studies, there are some significant challenges. One is the potential issue of confounding by indication, in this case, the issue of teasing out the effect of hypertension control on the risk for developing dementia. The authors tried to address this by adjusting for blood pressure control during the 3-year follow-up; however, this does not provide a sufficient explanation and needs to be discussed further, for example, by stratification by blood pressure control. The other issue is multiple antihypertensive medication use or changing antihypertensive medication groups during the follow-up period; sorting these factors would require large studies. Ding et al. report that approximately 73% of their participants reported multiple antihypertensive medication use in the AT1RB group, which limits interpretation. Last, as midlife hypertension is widely recognized to be more predictive of late-life dementia, most studies on the older population, including the present study, do not address a history of hypertension or antihypertensive medication use prior to enrollment.

The damaging effects of hypertension are mediated by cerebrovascular disease; however, few studies have evaluated how specific antihypertensive medication groups could alter cerebrovascular disease and how this could affect dementia risk.[4]

One central question will always remain: whether these antihypertensive medications exert their protective effect through their blood pressure-lowering effect, a direct effect independent of the blood pressure-lowering effect, or both. A possible way to answer this question is to have a longitudinal study starting in midlife with a large sample size, long follow-up, and information on incident cerebrovascular disease through the study to perform mediation analysis.

Due to the limitations of observational studies, randomized controlled trials are needed. However, similar to observational data, meta-analyses of randomized controlled trials evaluating antihypertensive medication use for prevention found no significant risk reduction of dementia.[8,10] The lack of significant findings could be explained by dementia outcome being a secondary outcome; therefore, studies may not be sufficiently powered to capture effects, confounded by a large number of subjects loss-to-follow-up and a significant number of cross-over to active treatment of patients from placebo groups.[11] Having said that, there are currently numerous small ongoing randomized controlled trials with AT1RB

with cognitive function as an outcome to help inform larger trials.[11] One such study showed a superior effect of 12-month treatment with candesartan in people with hypertension and mild cognitive impairment compared to users of lisinopril in cognitive measures of executive function and verbal memory, and these effects were independent of blood pressure control.[12] A second randomized controlled trial with telmisartan for eight months in 62 cognitively normal, Black/African American middle-aged adults with a parental history of Alzheimer's disease was recently completed, and analyses of Alzheimer's disease cerebrospinal fluid biomarkers, cerebral blood flow, and cognition are underway. This raises another critical issue that needs to be addressed in the future in both observational studies and clinical trials: the underrepresentation of Black/African American participants at increased risk for hypertension and dementia.

There is emerging evidence for the renin angiotensin system involvement in Alzheimer's disease pathogenesis.[13] The renin angiotensin system generates multiple bioactive angiotensin peptides with a wide range of biological activities associated with the pathogenesis of Alzheimer's disease, either independently or in combination with blood pressure control, affecting vascular function and modulation of amyloid and tau metabolism.

Antihypertensive medication acting through the renin angiotensin system, in addition to their blood pressure-lowering effect, could exert their effect on the pathogenesis of Alzheimer's disease by multiple mechanisms, including antioxidant, anti-inflammatory, antithrombotic, anti-excitotoxicity, angiogenesis promoting effects, improvement of vascular endothelial function and modulation of amyloid and tau metabolism. Numerous in vitro studies have shown that angiotensin converting enzyme degraded amyloid beta, resulting in animal studies evaluating the effects of ACE-I on amyloid beta deposition and amyloid beta conversion.[13] However, results were conflicting, with some studies showing no effect after short-term treatment with captopril on amyloid beta degradation in young mice while increased amyloid deposition in old mice after long-term treatment with captopril. However, long-term captopril administration did not alter amyloid beta brain pathology in Alzheimer's disease transgenic mice.[13] Similarly conflicting findings were seen with other ACE-I such as enalapril and perindopril.[13]

Few studies have explored the neuropathological association between antihypertensive medication use in humans,[14] and only one study has done so in participants with mild cognitive impairment focusing on medications acting through the renin angiotensin system.[15] However, there are still many unanswered questions that need to be explored to understand better the exact mechanism by which these antihypertensive medications, such as AT1RB, exert their potential beneficial effect, such as measuring inflammatory markers, Alzheimer's disease biomarkers, endothelial markers and elucidating the role of renin angiotensin system by measuring components to understand its contribution in the development of Alzheimer's disease.

Studies on antihypertensive medication use and the potential impact on dementia risk inform possible mechanisms of action, such as identifying new pharmacological targets and biomarkers that could serve as predictors of cognitive decline and/or dementia.

The study by Deng et al.[1] fills part of this knowledge gap. It is the first study evaluating the impact of ATR1B medications on progression from mild cognitive impairment to dementia in people with hypertension accounting for Alzheimer's disease biomarkers. This study is markedly different from previous observational studies, and the two large meta-analyses focused on participants with normal cognition at baseline. Additionally, the availability of Alzheimer's disease biomarkers from the cerebrospinal fluid made it possible to help clarify the mechanism of ATR1B in the disease process. Another strength of their study includes the use of the Alzheimer's Disease Neuroimaging Initiative cohort, which has a large enough sample size to evaluate different antihypertensive medication groups, where participants had frequent and detailed cognitive evaluations over a 3-year period which allowed early detection of dementia. Thus, this study adds important new information to the literature on ATR1B and their potential beneficial effect on the progression of dementia, while additional studies should be done to better understand the exact mechanism.

## Sources of Funding and Disclosures

Sevil Yasar is supported by NIH grants 2U01HL096812-09 and 1R01AG07425801.

Whitney Wharton is supported by NIH grants 1R01AG066203-01 and 1RF1AG051514-01.

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