Can Preferentially Prescribing Angiotensin II Receptor Blockers (ARBs) over Angiotensin-Converting Enzyme Inhibitors (ACEIs) Decrease Dementia Risk and Improve Brain Health Equity?

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Currently, there are no effective disease-modifying treatments for Alzheimer’s disease and related dementias (ADRD) (National Institute on Aging, 2021). In this context, considerable attention has been given to prevention of ADRD. The 2020 report of the Lancet Commission on “Dementia Prevention, Intervention, and Care” estimated that modifying specific risk factors could prevent or delay up to 40% of ADRD globally (Livingston et al., 2020). Hypertension was one of 12 risk factors identified, responsible for an estimated 2% of all ADRD cases globally, and is the only modifiable risk factor for ADRD with randomized trial evidence showing lower risk of cognitive impairment by an intervention that improves the risk factor (i.e., blood pressure [BP] lowering) (Livingston et al., 2020; SPRINT MIND Investigators et al., 2019). The Department of Health and Human Services recently added a new goal to its National Plan to Address Alzheimer’s Disease, which focused on reducing risk factors, including hypertension (Office of the Assistant Secretary for Planning and Evaluation, 2021).

Underrepresented and socially disadvantaged populations are disproportionately affected by both hypertension and ADRD. Therefore, a fundamental approach to improving ADRD prevention and brain health equity is improving hypertension awareness, treatment, and control across all groups. Randomized trial evidence shows that lowering BP with antihypertensive medication reduces the risk of cognitive impairment. More intensive BP control can be equitably achieved across underrepresented groups when provided using a standardized, well-resourced, and team-based approach (Adams and Wright, 2020; SPRINT MIND Investigators et al., 2019; Jaffe et al., 2013). Furthermore, certain classes of antihypertensive medication may reduce cognitive decline independent of their BP-lowering effects, which may augment the beneficial effects of BP lowering on ADRD risk. One group of antihypertensive medications of particular focus is renin-angiotensin-system (RAS) blockers—angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs)—which are used by approximately 32.5 million U.S. adults and are recommended interchangeably by current U.S. BP guidelines (CDC, 2022; Whelton, 2018). ACEIs act by inhibiting the conversion of angiotensin I to angiotensin II, lowering circulating angiotensin II and thereby reducing BP. ARBs, in contrast, directly antagonize the angiotensin II type 1 (AT1) receptor, which is downstream in the RAS from where ACEIs act, leading to reduced BP as well as shifting circulating angiotensin II to bind and stimulate AT2 and AT4 receptors. Angiotensin II stimulating AT2 and AT4 receptors has been shown to reduce oxidative stress and neuroinflammation, and improve cerebral hypoperfusion, potentially leading to memory-enhancing effects (Afsar et al., 2021; Villapol and Saavedra, 2015; Saavedra, 2012). Thus, if the hypothesis that ARBs have beneficial cognitive effects over ACEIs is proven true, there could be a benefit on brain health equity. The goal of this commentary is to describe (1) how increasing BP treatment and control with specific antihypertensive medication classes (ARBs) may reduce popula-
tion-level dementia risk while improving brain health equity and (2) the estimated benefits such a shift (from ACEI to ARB) would have for underrepresented groups.

**Disparities in Hypertension and ADRD**

Both hypertension and ADRD disproportionately affect underrepresented groups. In 2018, the age- and sex-adjusted prevalence of hypertension (defined as systolic/diastolic BP ≥ 140/90 mm Hg) was substantially greater in non-Hispanic Black (45%) than in non-Hispanic White adults (31%) (Aggarwal et al., 2021). Black adults develop hypertension earlier in life, have higher average BP, and, in the context of usual care, are less likely to achieve BP control than other racial and ethnic groups despite similar treatment rates (Hardy et al., 2021). Similarly, compared to non-Hispanic White adults in the United States, Hispanic adults have higher mean BP and are less likely to achieve BP control (Aggarwal et al., 2021). At the same time, disparities in ADRD are equally striking. The incidence of ADRD is nearly two times higher among older Black adults and about 1.5-times higher among older Hispanic adults than older White adults in the United States (Alzheimer’s Association, 2020). Therefore, inadequate identification and treatment of hypertension is an important driver of the observed disparities in ADRD. The 2020 report of the Lancet Commission highlights some of the reasons for these disparities, including modifiable social determinants of health (e.g., education and air pollution) (Livingston et al., 2020).

**Hypertension Treatment and Control, Antihypertensive Medications, and ADRD**

Rates of BP control have declined recently in the United States, especially among underrepresented groups (Muntner et al., 2020). One factor contributing to the observed decline may be the suboptimal use of antihypertensive medications. For example, recent data show that 40% of U.S. adults with uncontrolled BP are taking only one antihypertensive medication class (Derington et al., 2020). Most patients with hypertension require two or more antihypertensive medication classes to achieve BP control (Derington et al., 2020). As such, current U.S. hypertension guidelines recommend initiating treatment with two or more antihypertensive medications in certain patients (Whelton, 2018), often necessitating the use of an ACEI or ARB in addition to calcium channel blockers or thiazide diuretics. However, evidence gaps remain as to whether (1) treatment with certain antihypertensive medication classes has greater beneficial effects on the brain beyond their BP-lowering effect and (2) there are racial and ethnic differences in cognitive benefits of specific classes of antihypertensive medications.

**Differential Effects of ARBs Versus ACEIs on Brain Health**

ARBs and ACEIs block distinct components of the RAS, a complex biochemical pathway critical to the regulation of BP and shown to have an integral role in the pathogenesis of cardiovascular disease and ADRD (Kehoe, 2018). As a result, ARBs and ACEIs have different effects on physiologic abnormalities in hypertension (e.g., vasoconstriction, inflammation, fibrosis, and oxidative stress). Current hypertension guidelines recommend ARBs and ACEIs interchangeably due to presumed equivalent BP-lowering effects and cardiovascular event reduction (both overall and within racial/ethnic groups) (Messerli et al., 2018; Whelton, 2018). Recent observational data support that ARBs, compared with ACEIs, may be safer and equally effective at cardiovascular disease event reduction (Chen, 2021).

While mechanistic and clinical (human) data support the hypothesis of a comparative beneficial cognitive effect of ARBs over ACEIs, there is currently limited observational and trial data. The distinctive downstream pharmacologic effects of ARBs compared to ACEIs may result in differential long-term risk of ADRD. However, limited randomized trial data directly compare the effectiveness of ARBs and ACEIs on adjudicated cognitive outcomes. The best available data come from a network meta-analysis of 13,734 patients (mostly people of European ancestry) across 19 randomized controlled trials, which found that ARBs were superior to ACEIs in preventing cognitive decline (Marpillat, 2013). Moreover, a meta-analysis of 12 randomized clinical trials including 96,158 participants found that BP lowering with antihypertensive medication reduced risk of incident dementia or cognitive impairment (absolute risk reduction, 0.39%) (Hughes, 2020). However, existing studies are limited by relatively short duration of follow-up, insufficient sample size to evaluate subgroups (e.g., racial and ethnic minorities) for effect modification, and not evaluating adjudicated mild cognitive impairment (MCI)—a transitional state to dementia.

The potential implications of switching ACEIs to ARB use are sizable. Approximately 73% of U.S. adults with hypertension and prescribed antihypertensive medication (i.e., 44.3 million) are taking an ARB (13.5 million) or ACEI (19.1 million) annually (CDC, 2022). Given the
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The prevalence of hypertension and ACEI use (2.5 million Black U.S. adults using an ACEI), even if ARBs are only 10%–15% more effective than ACEIs at preventing ADRD, switching first-line RAS-blockade from ACEIs to ARBs could have an impact on population health and improve brain health equity. For context, one micro-simulation analysis (2010–2050) found that if an intervention delayed ADRD onset by five years, the prevalence of ADRD would go down by 41%, and costs would be reduced by 40% (Zissimopoulos, 2014).

What Strength of Evidence Is Needed to Make This Shift?

A central challenge to implementing preferential prescribing of ARBs over ACEIs is determining the level of evidence needed to make the recommendation. While randomized controlled trials provide the strongest evidence for estimating causal effects of treatments, dementia prevention trials targeting mid-life risk factors, such as hypertension, would be cost and time prohibitive as they would need to have enormous sample sizes and be decades in length to observe sufficient outcomes to generate meaningful inferences. Such trials are unlikely to occur in the near term. More feasible, cost- and time-efficient study designs could include a quasi-experimental (e.g., instrumental variable) approach, or smaller pilot trials using intermediate outcomes such as ADRD blood or brain imaging biomarkers or measures of cognitive function. In addition, a large pragmatic trial using dementia outcomes documented in medical records as part of routine clinical care could also be pivotal.

Context-Specific Evidence Thresholds for Prescribing Decisions

Another factor to consider is the risk-benefit context of a particular clinical situation or decision. The principal question is, “Do we need to wait for more randomized trial evidence to make this treatment switch?” The authors offer the opinion that we do not need to wait and have enough evidence to act now. In this situation, context-specific evidence thresholds should be applied. In the current health care landscape for the treatment of hypertension to reduce risk of ADRD, the following knowledge exists:

1. ARBs and ACEIs have similar efficacy in terms of BP-lowering and cardiovascular disease event reduction (Chen, 2021);
2. ARBs have a more favorable safety profile than ACEIs (i.e., lower risk of cough and angioedema) (Chen, 2021), especially among underrepresented groups;
3. Short-term RCT data suggest a comparative benefit of ARBs over ACEIs in preventing cognitive decline (Hajjar et al., 2020);
4. There is strong biological plausibility of a beneficial effect of ARBs over ACEIs in preventing cognitive decline (Kehoe, 2018);
5. Mounting observational data suggest a benefit of ARBs over ACEIs in preventing cognitive decline (den Brok et al., 2021; Marcum et al., 2022; van Dalen et al., 2021); and

Given this context, the evidence threshold for preferential prescribing of ARBs over ACEIs for hypertension management and for reducing the risk of cognitive decline should be lower than most other treatments in medicine. Future research is needed to understand why ACEIs and ARBs have similar effectiveness for cardiovascular event reduction but possibly different effectiveness for ADRD risk reduction.

Moreover, given the high prevalence of hypertension overall and the frequent use of antihypertensive medications, even a modest relative benefit of ARBs might reduce population-level dementia risk and improve brain health equity by switching first-line hypertension treatment from ACEIs to ARBs. Moreover, hypertension disproportionately affects underrepresented groups, particularly in mid-life, and the risk of ADRD is substantially higher in these groups. Thus, the potential contribution of this shift in antihypertensive prescribing toward achieving health equity is substantial.

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