Antihypertensive medications and dementia in older adults with hypertension.

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Antihypertensive medications and dementia.

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ABSTRACT

Background: Studies on middle-aged or individuals with cognitive or cardiovascular impairments, have established that intensive blood pressure (BP) control reduces cognitive decline risk. However, uncertainty exists on differential effects between antihypertensive medications (AHM) classes on this risk, independent of BP-lowering efficacy, particularly in community-dwelling hypertensive older adults.

Methods: A post-hoc analysis of the ASPREE study, a randomized trial of low-dose aspirin in adults aged 70+ years (65+ if US minorities) without baseline dementia, and followed for two years post-trial. Cox proportional-hazards regression models were used to estimate associations between baseline and time-varying AHM exposure and incident dementia (an adjudicated primary trial endpoint), in participants with baseline hypertension. Subgroup analyses included prespecified factors, APO ε4 carrier status and monotherapy AHM use.

Results: Most hypertensive participants (9,843/13,916; 70.7%) used AHMs. Overall, 'any' AHM use was not associated with lower incident dementia risk, compared with untreated participants (HR 0.84, 95%CI 0.70-1.02, p=0.08), but risk was decreased when angiotensin receptor blockers (ARBs) were included (HR 0.73, 95%CI 0.59-0.92, p=0.007). ARBs and β-blockers decreased dementia risk, whereas angiotensin-converting enzyme inhibitors (ACEIs) and diuretics increased risk. There was no association with RAS modulating or blood-brain-barrier crossing AHMs on dementia risk.

Conclusions: Overall, AHM exposure in hypertensive older adults was not associated with decreased dementia risk, however, specific AHM classes were with risk direction determined by class; ARBs and β-blockers were superior to ACEIs and other classes in

decreasing risk. Our findings emphasize the importance of considering effects beyond BP-lowering efficacy when choosing AHM in older adults.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

ACEI	Angiotensin Converting Enzyme inhibitor	**AHM**	Anti-Hypertension Medication
APOE ε4	Apolipoprotein E, variant ε4	**ARBs**	Angiotensin receptor blocker
ASPREE	ASPirin in Reducing Events in the Elderly	**ASPREE-HTN**	ASPREE Hypertension population
ASPREE-XT	ASPREE eXTension observational study	**AT1/AT2/AT4**	Angiotensin II receptor type 1 / 2 / 4
ATC code	Anatomical Therapeutic Chemical code	**BB**	Beta-Blocker
BBB	Blood-brain-barrier	**CCB**	Calcium Channel Blocker
CES-D 10	Centre for Epidemiologic Studies-Depression, 10 item scale	**DBP**	Diastolic blood pressure
HTN	Hypertension	**RAS**	Renin Angiotensin System
SBP	SBP = Systolic blood pressure	**TC**	Total cholesterol.
3MS	Modified Mini Mental Examination		

INTRODUCTION

Dementia affects an estimated 55 million individuals globally, and expected to reach 70 million and 139 million by 2030 and 2050, respectively.[1] The risk and prevalence of dementia increases with age, without an apparent ceiling.[2] Hypertension, one of the most prevalent and modifiable risk factors for dementia,[3] also increases in prevalence with age,[4] leading to older adults accounting for the bulk of hypertension-related morbidity and mortality.[5] Hypertension can directly impact cognition through increased risk for stroke and subsequent post-stroke cognitive impairment ,[6] but also indirectly by hypertension-related changes in the cerebral vasculature, impairing cerebral perfusion and inducing inflammation and tissue damage.[7] The treatment of hypertension in older adults is therefore a public health priority.

Despite existing comprehensive reviews on hypertension's pathophysiology and links to dementia,[8-10] evidence on the relationship between hypertension, treatment strategies and dementia in the very old (>80 years) remains limited[8] and inconsistent.[10,11] These inconsistencies are partly driven by the study population (e.g., cognitively intact, mildly impaired or with dementia or CVD), but also by the varying effects of individual antihypertensive medications (AHM) classes on dementia, independent of their blood-lowering effect.[10,12-15] For example, prior studies found that renin-angiotensin system (RAS) inhibitors, (angiotensin II receptor type 1 (AT1) blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEIs)), had the potential to reduce dementia risk or progression from mild cognitive impairment to dementia,[13,15] whilst many have reported no clear association.[16,17] It remains unclear whether the association its directionality, with the

development and progression of dementia differs between AHM class, especially ACEIs and ARBs,[18-22] in older cognitively intact adults.

Using the comprehensive cognitive and medication use data collected in the ASPirin in Reducing Events in the Elderly (ASPREE) trial[23,24] and extended 2 years post-trial period, ASPREE-XT,[25] we conducted a post-hoc analysis in community-dwelling, cognitively intact older adults who had hypertension at trial entry, to determine: (1) the associations of baseline and time-varying AHM use with long-term incident all-cause dementia; (2) the role of AHM class, including RAS modulation or blood-brain-barrier penetrance, in mediating AHM-related dementia risk; and (3) the extent that mono- and/or combination-AHM use, or APOE ε4 carrier status, were associated with changes in the risk profile.

METHODS

Data Availability and Study Population

The authors declare that all supporting data are available within the article, and its online supplementary files. Researcher access to the ASPREE study longitudinal dataset is via application through the ASPREE data access management system (https://ams.aspree.org/application/home.aspx).

This is a post-hoc analysis of data from the ASPREE study. Details on study design, recruitment, and baseline population characteristics at clinical trial enrolment and entry into the observational extension (ASPREE-XT) have already been described.[23-25] ASPREE was a prospective, randomized placebo-controlled trial comparing effects of daily low-dose aspirin

(100mg) versus placebo, on disability-free survival. Briefly, 19,114 healthy, community-dwelling people aged ≥70 years (≥65 years for US minorities) were randomized in Australia (n=16,703, 87%) and the US (n=2,411, 13%) from March 2010 to December 2014. The trial concluded in June 2017 (median follow-up 4.7 years, IQR, 3.6-5.7) and involved annual in-person study visits between 2011 and 2017. Eligible participants were free from evidence of cardiovascular disease (CVD), independence-limiting physical disability, and expected to survive for at least 5 years. Individuals with persistent severe hypertension (defined as ≥180 and/or ≥105 mmHg), a self-report or physician diagnosis of dementia, or a Modified Mini-Mental State Examination (3MS)[26] score of <78/100, were ineligible. Participants provided informed consent and local ethics committees approved the study.

Participants with known baseline hypertension (HTN; defined as systolic/diastolic blood pressure [SBP/DBP] of <180 -≥140 and/or <105 -≥90 mmHg and/or self-report of AHM use) were included in this analysis and followed through to the second study visit post-trial (observational phase), median [IQR] follow-up: 6.4 [5.3-7.6] years).

Exposure to Antihypertensive Medications (AHMs)

Participants brought all currently used medications, a list or self-report of medications, to annual visits, with subsequent confirmation via primary care practice medical records. Participants were sorted by baseline AHM use (treated vs untreated) and by AHM class. The 'untreated' group comprises those with HTN who did not use any AHM at baseline. AHMs were classified according to their primary mode of action: ARBs; ACEI; diuretics; Calcium Channel Blockers (CCBs); and β-blockers (BBs). Other, less frequently used AHMs (n=549, ATC codes beginning with 'C02') were excluded from analyses by class, but included in combination therapy. AHMs were also categorized by whether they were RAS stimulating or

inhibiting.[20] Determination of blood-brain-barrier (BBB)-crossing potential was established following previous literature.[27]

Ascertainment of dementia

All-cause incident dementia was defined according to the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) criteria, [28] and details previously outlined.[24] Briefly, suspected cases of dementia (3MS score ≤77/100 or drop of >10.15 points from the predicted 5-year age- and education-adjusted score, reported cognitive concerns in medical records, a clinician diagnosis of dementia, or prescription of cholinesterase inhibitors) were referred for further cognitive assessment and then adjudicated by an expert panel blinded to treatment assignment.

Assessment of covariates

Baseline confounders were selected based on known associations with dementia and potential interaction effects with AHMs.[29] Model 1 adjusted for age and sex, and Model 2 further adjusted for race/ethnicity (White, Black, Hispanic/Latino, Others [includes Australian aborigine/Torres Strait islander, native American, more than one race, native Hawaiian/Pacific Islander and non-Hispanics who did not state their ethnicity/race]), country (Australia, US), years of education (<12, ≥12 years), smoking status (never, former, current), alcohol consumption (never, former, current), mean total cholesterol, living alone (yes/no), polypharmacy (≥5 prescription medications), family history of dementia (self-report), chronic kidney disease (CKD; estimated glomerular filtration rate <60 ml/min/1.73m^2 or urinary albumin-to-creatinine ratio ≥3mg/mmol), diabetes (self-report or fasting glucose ≥ 126mg/dL or glucose-lowering medication use), statin use, baseline composite cognitive z

scores (see Appendix S1 for calculation), depression score (8+/30) measured by the Center for Epidemiologic Studies Depression 10-item Scale (CES-D 10),[30] baseline SBP and DBP, and ASPREE randomized treatment (aspirin/placebo). Procedures for covariate assessments are described in the ASPREE protocol (https://aspree.org/). Results are discussed for the fully adjusted model (Model 2), unless otherwise indicated.

Statistical analyses

Descriptive statistics (frequencies (%) and means (SDs)) were used to summarize AHM prevalence in the ASPREE-HTN population. Cox proportional-hazards regression models were used to estimate the association between baseline AHM exposure (by 'any' exposure [yes/no], by monotherapy and/or combination therapy, by class [ARBs, ACEI, diuretics, CCB, BBs] and by RAS-stimulating or -inhibiting capability and BBB penetrance) and incident dementia. Participants were followed until the occurrence of dementia, death, or end of follow-up, whichever occurs first. Proportional-hazards assumptions were checked using Schoenfeld residuals test and no violations were detected. We repeated all analyses for incident dementia by treating AHM use for each class as a time-varying variable. Sensitivity analyses were conducted in a sub-cohort with known APOE ε4 genotype carrier status (10,538 genotyped; with 2684 ε4 carriers), further adjusting Model 2 for APOE ε4 status (Model 3), which did not change the main findings. We also repeated the main analysis with a 2-year lag period excluding participants with follow-up time or incident dementia <2 years from the baseline to avoid the potential reverse causation.

All p-values were two-sided and $p<0.05$ was considered as significant. Analyses were performed using Stata/SE (StataCorp, version 15.0).

RESULTS

Participants without HTN (n=4,919) and those with missing values for baseline composite cognitive test scores (n=133) and for baseline covariates (n=147,) were excluded from this analysis, leaving 13,916 hypertensive participants included in the study sample (herein called ASPREE-HTN; **Supplementary Figure S1**).

Participant baseline characteristics.

ASPREE-HTN participant (N=13,916) characteristics by baseline AHM use are presented in **Table 1**. The mean [SD] age was 75.3 [4.6] years, 55.8% were female, 9,843 (70.7%) were taking AHMs at baseline, and of the AHM users, 48.2% used ARBs, 32.4% used ACEIs, 15.5% used BBs, 35.3% used diuretics and 32.9% used CCBs. ARB use was lowest in Blacks and Hispanics/Latinos (27.6% and 27.3%, respectively), compared to Whites (50%), with CCB and diuretics more common in Blacks (44.6% and 56%, respectively) and ACEIs most common in Hispanic/Latinos (49.5%). Additionally, 99.4% (n=9,782) remained on at least one AHM at each annual visit throughout follow-up. Compared to baseline untreated HTN participants, AHM users were more likely to be female, Black, never to have consumed alcohol, had a lower average education level, lived alone, had a higher prevalence of diabetes and CKD, polypharmacy and statin use (**Table 1**). The majority were using only one AHM (49.5%), with 35% using 2 AHMs and 15.5% using ≥3. Importantly, the prevalence of family history of dementia and APOE ε4 carrier status was similar across all AHM groups. Of the 'untreated group' (n=4073), 50.5% were prescribed an AHM at some stage during follow-up (**Supplementary Table 1**).

Baseline characteristics of participants without hypertension (excluded from this analysis) or who used AHM monotherapy, are shown in **Supplementary Tables 2 and 3**, respectively.

Compared to those without HTN, those with HTN had higher prevalence of CKD, diabetes, statin use and polypharmacy (**Supplementary Table 2**).

AHM use and incident dementia

Table 2 shows a comparison between specific AHM-treated hypertensive groups (as monotherapy or in combination with other AHMs) vs the untreated group, on dementia risk. During follow-up, there were 638 incident dementia cases; 193/4,073 (4.7%) in the untreated group and 445/9,843 (4.5%) in the treated group. Compared with no use, any-AHM use was not associated with a significant change in dementia risk (Model 2 [fully adjusted] HR 0.84, 95% CI 0.70-1.02; p=0.08). Adjusting for APOE ε4 carrier status or introducing a 2-year lag did not alter these findings (**Supplementary Table 4 and Table 5**).

When examining specific AHM classes, ARB use, as monotherapy or in combination, compared to the untreated group, was associated with a significant decrease in dementia risk; HR 0.75, 95% CI, 0.57-0.99, p=0.04 and HR 0.72, 95% CI, 0.56-0.94, p=0.02, respectively. BBs use in combination with other AHMs was significantly associated with decreased risk of dementia ('any' BB, HR 0.73, 95%CI, 0.53-0.99, p=0.04 and in combination with another AHM, HR 0.71, 95%CI, 0.51-0.99, p=0.046), but not for monotherapy use (HR 0.79, 95%CI, 0.45-1.39, p=0.41).

We compared specific AHM classes against each other to determine which AHM had the greatest impact on dementia risk, conducting the comparison as either 'any' specific AHM class (*i.e.,* monotherapy and/or combined with any other class**, Table 3A**) or as monotherapy only (**Table 3B**). ARB use, either 'any' or as monotherapy, was associated with a significantly lower dementia risk compared to ACEIs (by 27% and 31%, respectively) or to

CCBs (by 27% and 33%, respectively). Any BB AHM use was associated with a reduction (35%) in dementia risk compared to ACEIs (**Table 3A**).

AHM mode of action and dementia

We further explored whether AHM classes, categorized (without cross over) by their mode of action, had differential effects on dementia risk (**Table 4**). AHMs were categorized as either exclusively AT2/AT4 receptor-stimulating or -inhibiting, or by the ability to cross the blood-brain-barrier (BBB) (**Supplementary Table 6**). There was a trend towards a lower dementia risk with AT2/AT4 receptor-stimulating AHMs, compared to AT2/AT4 receptor-inhibiting AHMs, although this association was not statistically significant (HR 0.78, 95%CI 0.59-1.03, p=0.08). Within the AT2/AT4 receptor-stimulating group, ARB use was associated with a significantly decreased dementia risk compared to the AT2/AT4 receptor-inhibiting AHMs (HR 0.74, 95%CI 0.57-0.95, p=0.02), and a numerically, but not statistically significant lowered risk of dementia with thiazides (HR 0.77, 95%CI 0.56-1.05, p=0.10). BBB penetrance did not modify the association with dementia risk when comparing ARBs to ACEI classes (**Table 4**).

Time-varying analysis of AHM use and incident dementia

When treating AHM class as a time-varying variable, use of ARBs, compared to other AHMs, was associated with a significant decreased dementia risk (by 24%, 31%, and 20%, for 'any', mono- or combo-therapy, respectively) (**Figure 1**). Conversely, ACEIs were associated with increased dementia risk by 21% for 'any' ACEIs, and whilst the trend for increased risk remained with mono- and combo-ACEI therapy use (by 29% and 17%, respectively), significance was lost. No other AHM class was associated with dementia risk over time.

DISCUSSION

In this post-hoc study of 13,916 hypertensive ASPREE participants followed for a median of 6.4 years, we found that compared with untreated hypertensive participants, 'any' baseline AHM use was not significantly associated with a change in incident dementia risk; however, when examined by AHM class, ARB use at baseline, as either combination or monotherapy, was associated with significantly decreased risk of dementia. β-Blockers were also associated with a decreased dementia risk compared to other classes, although this was only apparent when in combination with other AHMs. ARBs were associated with the greatest reduction in dementia risk compared to any other class. No other AHM class was associated with a significant change in dementia risk, although point estimates for ACEIs and CCBs trended towards harm when in monotherapy, and diuretics trended towards benefit. The time varying analysis exploring AHM exposure throughout follow-up supported the baseline exposure data, confirming the reduced dementia risk from ARB exposure at any stage during follow-up, and the increased risk with ACEIs, regardless of whether in combination or monotherapy. The differential impacts of the different AHMs account for the null finding with 'any' AHM use observed in this study.

Prior reports describing neuroprotection and AHMs have been inconsistent. Some observational studies and RCTs reported no significant neuroprotection with AHM use either in individuals with[31] or without mild cognitive impairment (MCI)[32] at baseline. Other studies have reported overall benefits of 'any' AHM use or class specific benefits.[33-36] Finally, other studies have reported detrimental effects on cognition.[16,17] Study sample size and risk profile (*e.g.,* differences in prior CVD or stroke, pre-existing hypertension, diabetes, mild

cognitive decline, MCI, or dementia at baseline), comparator groups (*e.g.,* normotensive, untreated or treated hypertensive individuals, by specific AHM only), length of follow-up and differences in outcomes (MCI vs dementia) and their mode of ascertainment, may all contribute to these varied findings.[19,20] For example, previous randomized trials reported no significant neuroprotective effects of AHM use when compared with placebo or benefits from specific AHM class in between-class comparisons.[17,37]

Whilst the strength of the evidence in these RCTs is limited by short follow-up, small sample size and younger study populations, larger more recent meta-analyses utilizing individual participant data also did not find significant AHM class differences when compared to all other AHMs combined.[21,22] In contrast, in a large study of over 128,683 hypertensive patients with MCI, all five major classes of AHM showed a protective effect against progression to Alzheimer's disease-related dementia (ADRD) compared to AHM users except of the AHM class being examined.[31]

Many studies have reported both ARBs and ACEIs confer similar neurocognitive benefits,[38-40] whilst others have reported increased dementia risk with ACEIs use[41,42] or no effect.[43,44] Additionally, a number of large meta-analyses and studies have reported that ARBs are superior to other classes in decreasing dementia risk: when compared to diuretics, BB or CCBs[45]; when compared to all-AHMs and ACESIs[44]; and when compared to ACEIs[46], although this last study reported BBs, CCBs and diuretics were superior to ARBs.

Our findings are in line with studies reporting neurocognitive benefits with ARBs and not ACEIs.[13,18,44,47] We observed a 25-30% decreased dementia risk with ARB use when compared to the untreated group or directly with ACEIs (monotherapy or combination ACEIs), similar to the 20-22% risk reduction reported by others.[44,47] When comparing ACEIs

to the untreated group, we did not observe any significant outcomes, although there was a significant higher dementia risk when ACEI use was treated as a time-varying variable (P=0.04). Additionally, when ACEIs were compared to other AHM classes, a significant increased risk was observed, particularly compared to ARBs (by 37% and 45% for combination and monotherapy ACEI use, respectively).

Mechanism

Evidence suggests that differences in dementia risk across various AHM classes may be explained by their differential impact on modulating type 2 and type 4 angiotensin II receptors and ability to penetrate the blood-brain barrier.[19,20,48] ARBs block angiotensin-II AT1 receptors and cause upregulation of AT2 and AT4 receptors,[49] which may promote cerebral perfusion and neurite growth, decrease vascular dysfunction and inflammation, and reduce amyloid-β and associated cholinergic deficiency–factors involved in dementia pathogenesis.[12,27] In contrast, increased bradykinin levels resulting from ACEIs is proposed to worsen cognition, and has been linked to AD pathology.[50] Bradykinin increases vascular permeability, stimulates prostaglandin synthesis (promoting inflammation), and increases ROS levels (associated with neuronal damage and accumulation of toxic amyloid-β).[50,51] Higher amyloid-β accumulation has been reported in the cerebral cortex of cognitively normal adults using ACEIs, compared to ARBs users,[52] aligning with our findings of increased dementia risk with ACEIs.

A lower risk of incident cognitive impairment and dementia has been reported with AT2/AT4 receptor-stimulating AHMs when compared with AT2/AT4 receptor-inhibiting AHMs,[19,20,46] and with BBB-crossing RAS medications,[42] while one study reported an increased risk with BBB-penetrance.[53]

We found AT2/AT4 receptor-stimulating AHMs compared to AT2/AT4 receptor-inhibiting AHMs, did not reach significance in reducing dementia risk, but trended to benefit (HR=0.77, 95% CI 0.56-1.05, P=0.10), reaching significance when ARBs were isolated within the AT2/AT4 receptor-stimulating group (HR=0.73, 95%CI 0.57-0.95, P=0.02). Our data suggests that AT2/AT4 receptor-stimulating AHMs may lead to decreased dementia risk compared to AT2/AT4 receptor-inhibiting AHMs, and thus, provide a mechanism of action for the neurocognitive effects of ARBs based on the angiotensin receptor hypothesis. However, we found no association with BBB penetrance, in line with other studies.[40,43]

Study strengths and limitations

This study has several strengths. It utilizes a well described, phenotypically rich, large 'real-world' cohort of older adults with HTN (median age 74), without severe cognitive impairment and/or persistently high hypertension (180/105 mmHg) at enrolment and followed annually for median 6.4 years. Self-reported prescription medication use was confirmed by physical confirmation and medical record review. Dementia was a pre-specified study outcome and adjudicated by expert panel, utilizing evidentiary documentation. To remove the impact of BP and hypertension on dementia risk, we only included hypertensive participants and adjusted for baseline SBP and DBP. We compared AHM exposure to untreated and treated groups, as well as direct class-to-class comparisons and repeated this in a subgroup with known APOE e4 carrier status.

Several limitations should also be noted. This study is observational and therefore may be biased by residual confounding, in addition to possible indication bias. Neither AHM dose nor prior duration of use were recorded in ASPREE, thus, the long-term association on dementia risk of AHMs could not be explored. Subgroup analyses may only have modest

power to detect associations in selected subgroups and the significance of the interactions between AHM use and stratification variables. Since all ASPREE participants were free of dementia at trial entry and were generally healthier than the wider older population, our findings cannot be generalized to subjects with either MCI or dementia, and those with major multimorbidity.

Conclusion

In this hypertensive community-dwelling older adult population, compared with non-use, any AHM use was not associated with change in risk of incident dementia. However, specific AHM classes were associated with change in risk, and its direction (benefit vs harm) was driven by AHM type, with ARBs and diuretics associated with lower risk, and ACEIs associated with higher risk. These findings appeared to be linked to AT2/AT4 receptor-stimulating AHMs but did not differ by blood-brain barrier permeability. The study results must be interpreted with caution due to the study's observational nature and will require confirmation by randomized clinical trials designed to explore the effects of AHMs on dementia risk in healthy older populations, in those at higher risk of dementia or with MCI and/or CVD.

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DISCLOSURES

Dr. Shah reports being the site principal investigator or sub-investigator for Alzheimer's disease clinical trials for which his institution (Rush University Medical Center) is compensated [Amylyx Pharmaceuticals, Inc., Athira Pharma, Inc., Edgewater NEXT, Eli Lilly & Co., Inc., Genentech, Inc.]. The remaining authors declare that they have no conflict of interests.

Supplementary Material:

Supplemental Methods,

Figure S1

Tables S1-S6

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TABLES

Table 1. Hypertensive cohort (ASPREE-HTN) baseline characteristics between antihypertensive medication (AHM) treated (not mutually exclusive) and untreated groups.

Characterisitic*	Overall (n=13916)	Untreated (no AHM) (n=4073)	Treated (Any AHM) (n=9843)	Class of Antihypertensive Medication				
				ARB (n=4747)	ACEI (n=3188)	CCB (n=3240)	Diuretic (n=3470)	β-blocker (n=1521)
Age, mean ± SD	75.3 ± 4.6	75.1 ± 4.5	75.4 ± 4.7	75.4 ± 4.5	75.1 ± 4.6	75.5 ± 4.8	75.3 ± 4.8	75.5 ± 4.9
Female (% of column)	7762 (55.8)	1933 (47.5)	5829 (59.2)	2912 (61.3)	1708 (53.6)	1871 (57.8)	2290 (66.0)	1051 (69.1)
Race								
White	12468 (90.9)	3826 (93.9)	8822 (89.6)	4415 (93.0)	2802 (87.9)	2844 (87.8)	2997 (86.4)	1280 (84.2)
Black	702 (5.0)	104 (2.6)	598 (6.1)	165 (3.5)	210 (6.6)	267 (8.2)	335 (9.7)	168 (11.1)
Hispanic/Latino	355 (2.6)	82 (2.0)	273 (2.8)	88 (1.9)	135 (4.2)	80 (2.5)	89 (2.6)	54 (3.6)
Others	211 (1.5)	61 (1.5)	150 (1.5)	79 (1.7)	41 (1.3)	49 (1.5)	49 (1.4)	19 (1.3)
Country								
Australia	12265 (88.1)	3711 (91.1)	8554 (86.9)	4437 (93.5)	2666 (83.6)	2781 (85.8)	2841 (81.9)	1165 (76.6)
U.S.	1651 (11.9)	362 (8.9)	1289 (13.1)	310 (6.5)	522 (16.4)	459 (14.2)	629 (18.1)	356 (23.4)
Smoking								
None	7632 (54.8)	2174 (53.4)	5458 (55.5)	2640 (55.6)	1717 (53.9)	1792 (55.3)	1965 (56.6)	920 (60.5)
Former	5763 (41.4)	1729 (42.5)	4034 (41.0)	1958 (41.3)	1353 (42.4)	1390 (40.4)	1385 (39.9)	565 (37.2)
Current	521 (3.7)	170 (4.2)	351 (3.6)	149 (3.1)	118 (3.7)	139 (4.3)	120 (3.5)	36 (2.4)
Alcohol consumption								
None	2485 (17.9)	577 (14.2)	1908 (19.4)	899 (18.9)	614 (19.3)	655 (20.2)	745 (21.5)	344 (22.6)
Former	848 (6.1)	238 (5.8)	610 (6.2)	244 (5.1)	239 (7.5)	214 (6.6)	224 (6.5)	109 (7.2)

Current	10583 (76.1)	3258 (80.0)	7325 (74.4)	3604 (75.9)	2335 (73.2)	2371 (73.2)	2501 (72.1)	1068 (70.2)
Education (≥12 years)	7437 (53.4)	2305 (56.6)	5132 (52.1)	2362 (49.8)	1689 (53.0)	1688 (52.1)	1841 (53.1)	808 (53.1)
Chronic kidney disease	3895 (29.9)	848 (20.8)	3047 (33.0)	1519 (32.0)	977 (30.7)	1137 (35.1)	1137 (32.8)	552 (36.3)
Family history of dementia	3347 (24.1)	1022 (25.1)	2325 (23.6)	1095 (23.1)	736 (23.1)	741 (22.9)	855 (24.6)	348 (22.9)
Diabetes	1754 (12.6)	259 (6.4)	1495 (15.2)	720 (15.2)	624 (19.6)	561 (17.3)	550 (15.9)	264 (17.4)
SBP, mm Hg, mean ± SD	143.9 ± 15.8	151.8 ± 9.9	140.6 ± 16.6	140.4 ± 16.7	140.8 ± 16.7	141.4 ± 16.2	139.3 ± 16.5	140.4 ± 17.7
DBP, mm Hg, mean ± SD	78.8 ± 10.2	82.8 ± 8.9	77.1 ± 10.2	76.9 ± 10.5	77.2 ± 10.1	76.2 ± 10.1	76.4 ± 10.1	76.2 ± 10.7
TC, mmol/L, mean ± SD	5.2 ± 1.0	5.4 ± 1.0	5.1 ± 1.0	5.1 ± 1.0	5.0 ± 1.0	5.0 ± 1.0	5.1 ± 1.0	5.1 ± 1.1
Living alone	9339 (67.1)	2854 (70.1)	6485 (65.9)	3169 (66.8)	2116 (66.4)	2105 (65.0)	2237 (64.5)	932 (61.3)
Polypharmacy	4438 (31.9)	382 (9.4)	4056 (41.2)	2064 (43.5)	1137 (41.9)	1683 (51.9)	1943 (56.0)	874 (57.5)
CES-D, mean ± SD	3.2 ± 3.3	3.0 ± 3.3	3.3 ± 3.3	3.3 ± 3.3	3.2 ± 3.3	3.3 ± 3.4	3.4 ± 3.3	3.2 ± 3.3
Randomized aspirin	6910 (49.7)	1977 (48.5)	4933 (50.1)	2364 (49.8)	1610 (50.5)	1646 (50.8)	1770 (51.0)	771 (50.7)
Statin	4831 (34.7)	828 (20.3)	4003 (40.7)	1932 (40.7)	1385 (43.4)	1394 (43.0)	1485 (42.8)	694 (45.6)
Composite cognitive z score, mean ± SD	0.00 ± 0.71	0.06 ± 0.71	-0.02 ± 0.70	-0.01 ± 0.69	-0.06 ± 0.72	-0.06 ± 0.70	-0.02 ± 0.71	-0.07 ± 0.71
APOE ε4 carrier status								
Carrier	2684 (25.5)	832 (26.2)	1852 (25.1)	914 (25.0)	588 (25.5)	608 (25.4)	654 (25.7)	259 (24.5)
Non-carrier	7854 (74.5)	2340 (73.8)	5514 (74.9)	2737 (75.0)	1718 (74.5)	1784 (74.6)	1890 (74.3)	797 (75.5)
Number of AHMs								
1 only	4873 (35.0)	-	4873 (49.5)	1978 (41.7)	1343 (42.1)	619 (19.1)	447 (12.8)	363 (23.9)
2	3443 (24.7)	-	3443 (35.0)	1833 (38.6)	1219 (38.2)	1403 (43.3)	1787 (51.2)	496 (32.6)
3 or more	1527 (11.0)	-	1527 (15.5)	936 (19.7)	626 (19.6)	1218 (37.6)	1254 (36.0)	662 (43.5)
Other antihypertensive meds used in combination								

Any other AHM	NA	2769 (57.5)	1845 (57.9)	2621 (80.9)	3041 (87.2)	1158 (76.1)
ARB		0	118	1349	1755	552
ACE inhibitor		118	0	1009	1017	368
Calcium channel blocker		1349	1009	0	1116	496
Diuretics		1755	1017	1116	0	588
β blocker		552	368	496	588	0
Other†		192	142	212	171	110

*Data are presented as count (percentage) unless indicated.

† 'Other'= includes centrally-acting antiadrenergic agents, e.g. alpha-blockers (ATC codes begin with 'C02').

Table 2. Risk of incident dementia between treated (by 'any AHM' and by specific AHM class) and untreated groups in participants with baseline hypertension (ASPREE-HTN population).

Groups	Dementia Events (rate/1000 person-years)	Model 1 HR (95% CI)	P-value	Model 2 HR (95% CI)	P-value
Untreated group (n=4073)	193 (7.4)	1 (Reference)		1 (Reference)	
Treated (any AHM) group (n=9843)	445 (7.2)	0.99 (0.84-1.17)	0.92	0.84 (0.70-1.02)	0.08
Treated - Any ARB (n=4747)	183 (6.1)	0.85 (0.69-1.04)	0.12	**0.73 (0.59-0.92)**	**0.007**
ARB monotherapy (n=1978)	75 (6.0)	0.84 (0.64-1.09)	0.19	**0.75 (0.57-0.99)**	**0.04**
ARB plus other AHM(s) (n=2769)	108 (6.2)	0.86 (0.68-1.09)	0.22	**0.72 (0.56-0.94)**	**0.02**
Treated-Any ACEI (n=3188)	167 (8.4)	1.20 (0.97-1.47)	0.09	0.99 (0.79-1.24)	0.93
ACEI monotherapy (n=1343)	74 (8.8)	1.26 (0.96-1.64)	0.09	1.11 (0.84-1.47)	0.46
ACEI plus other AHM(s) (n=1845)	93 (8.1)	1.15 (0.90-1.47)	0.27	0.90 (0.69-1.18)	0.45
Treated - Any CCB (n=3240)	156 (7.8)	1.03 (0.83-1.27)	0.78	0.89 (0.71-1.13)	0.35
CCB monotherapy (n=619)	37 (9.5)	1.20 (0.85-1.72)	0.29	1.14 (0.80-1.63)	0.48
CCB plus other AHM(s) (n=2621)	119 (7.3)	0.99 (0.78-1.24)	0.91	0.83 (0.64-1.07)	0.14
Treated - Any diuretic (n=3470)	154 (7.0)	0.97 (0.79-1.21)	0.82	0.79 (0.62-1.01)	0.06
Diuretic monotherapy (n=447)	17 (5.9)	1.00 (0.94-1.07)	0.91	0.65 (0.39-1.09)	0.10
Diuretic plus other AHM(s) (n=3041)	137 (7.2)	**1.12 (1.11-1.14)**	**<0.001**	0.81 (0.63-1.05)	0.11
Treated - Any β-blocker (n=1521)	65 (6.9)	0.95 (0.72-1.26)	0.72	**0.73 (0.53-0.99)**	**0.04**
β-blocker monotherapy (n=363)	13 (5.7)	1.00 (0.95-1.06)	0.95	0.79 (0.45-1.39)	0.41
β-blocker plus other AHM(s) (n=1158)	52 (7.3)	**1.12 (1.11-1.14)**	**<0.001**	**0.71 (0.51-0.99)**	**0.046**

Table 3. Comparative risk of incident dementia in the AHM-treated hypertensive population between baseline use of different AHM classes, comparing each class (row versus column) as either 'any' use of the nominated class (Part A) or each class as monotherapy use (Part B).

A. Pairwise risk comparison between classes, with 'any' class use (*i.e.* used as monotherapy or in combination)

Comparison group / Treatment	ARB	ACEI	CCB	Diuretic	β-blocker (BB)
ARB	1	0.73 (0.58-0.91)	0.73 (0.56-0.96)	0.84 (0.62-1.15)	0.79 (0.56-1.11)
ACEI	1.37 (1.10-1.71)	1	1.17 (0.90-1.52)	1.33 (0.999-1.78)	1.53 (1.08-2.18)
CCB	1.37 (1.04-1.80)	0.86 (0.66-1.11)	1	1.21 (0.92-1.59)	1.37 (0.95-1.98)
Diuretic	1.19 (0.87-1.62)	0.75 (0.56-1.001)	0.83 (0.63-1.09)	1	1.06 (0.73-1.52)
β-blocker	1.26 (0.90-1.77)	0.65 (0.46-0.93)	0.73 (0.50-1.05)	0.95 (0.66-1.36)	1

B. **Pairwise risk comparison between monotherapy use of different AHM classes.**

Comparison group / Treatment	ARB	ACEI	CCB	Diuretic	β-blocker (BB)
ARB	1	0.69 (0.50-0.96)	0.67 (0.45-0.996)	1.06 (0.61-1.84)	0.94 (0.52-1.72)
ACEI	1.45 (1.04-2.01)	1	0.97 (0.65-1.45)	1.54 (0.89-2.67)	1.37 (0.75-2.49)
CCB	1.50 (1.003-2.24)	1.03 (0.69-1.55)	1	1.59 (0.88-2.87)	1.41 (0.74-2.68)
Diuretic	0.94 (0.54-1.63)	0.65 (0.37-1.12)	0.63 (0.35-1.13)	1	0.86 (0.43-1.84)
β-blocker	1.06 (0.58-1.93)	0.73 (0.40-1.33)	0.71 (0.37-1.34)	1.13 (0.54-2.35)	1

The estimate in the cell represents the pairwise comparison between the treatment AHM class (row) vs. the comparison group AHM class (column), with the analysis using Cox proportional-hazard models with Model 2. See Table 1 for sample sizes.

Participants who were taking both or none of the AHM classes involved in the comparison were excluded.

Green (HR< 1 & p<0.05) means a statistically significant lower risk of dementia in intervention group than control group, and orange (HR> 1 & p<0.05) means a statistically significant higher risk of dementia in intervention group than control group. Yellow (p≥0.05) means no statistically significant association between the two groups.

Table 4. Risk of dementia between baseline use of AHMs that inhibit vs stimulate type 2 and 4 Angiotensin II receptors, or cross vs non-cross the blood-brain-barrier.

Mechanisms	Events/Total (rate per 1000 person-years)	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value
AT modulating*					
AT 2/4-inhibiting AHM use	113/2169 (8.3)	1 (Ref)	-	1 (Ref)	-
AT 2/4-stimulating AHM use (Overall)	206/4934 (6.6)	**0.78 (0.62-0.98)**	**0.04**	0.81 (0.64-1.03)	0.09
Thiazides	70/1692 (6.5)	0.78 (0.58-1.05)	0.11	0.77 (0.56-1.05)	0.10
Dihydropyridine CCB	78/1578 (8.0)	0.91 (0.68-1.21)	0.52	0.98 (0.73-1.32)	0.89
ARB	155/3945 (6.3)	**0.75 (0.59-0.96)**	**0.02**	**0.74 (0.57-0.95)**	**0.02**
BBB penetrance and type of RAS medications†					
ACEI-based therapy					
Non-crossing BBB	21/376 (9.0)	1 (Ref)	-	1 (Ref)	-
Crossing BBB	144/2762 (8.4)	0.90 (0.57-1.42)	0.66	0.93 (0.58-1.48)	0.75
ARB-based therapy					
Non-crossing BBB	81/2260 (5.7)	1 (Ref)	-	1 (Ref)	-
Crossing BBB	99/2434 (6.5)	1.11 (0.83-1.49)	0.47	1.13 (0.84-1.53)	0.42
BBB crossing RAS medication					
ACEI-based therapy	139/2700 (8.3)	1 (Ref)	-	1 (Ref)	-
ARB-based therapy	94/2372 (6.3)	**0.73 (0.56-0.95)**	**0.02**	**0.76 (0.58-1.00)**	**0.046**
BBB non-crossing RAS medication					
ACEI-based therapy	21/368 (9.1)	1 (Ref)	-	1 (Ref)	-
ARB-based therapy	81/2252 (5.7)	0.59 (0.37-0.96)	0.03	0.64 (0.38-1.10)	0.11

*AT 2/4–inhibiting AHMs includes ACEIs, BBs, and non-dihydropyridine CCBs. AT 2/4–inhibiting AHMs are not mutually exclusive as monotherapy (*i.e.,* they could be in combination with other AHMs as long as it is another AT 2/4-inhibiting AHM). AT 2/4–stimulating AHMs includes thiazides, dihydropyridine CCBs, and ARBs. Only use of AT 2/4-stimulating AHMs were included in this category (as either monotherapy or in combination).

†Blood-brain-barrier (BBB) crossing ACEIs included captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril; BBB crossing ARBs included telmisartan, candesartan, valsartan; BBB non-crossing ACEIs included benazepril, enalapril, moexipril, quinapril; and BBB non-crossing ARBs included olmesartan, eprosartan, irbesartan, losartan.

FIGURE LEGEND

Figure 1. Risk of incident dementia between specific AHM treated groups (time-varying) over median 6.4 years of follow-up.

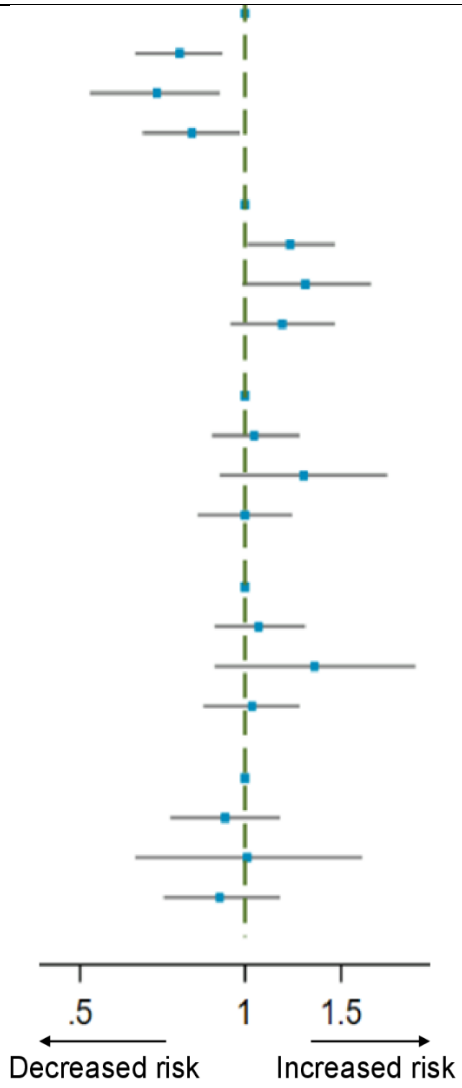
FINAL LIST OF DATA ELEMENTS

Number of tables: 4

Number of Figures: 1

Figure 1. Risk of incident dementia between specific AHM treated groups (time-varying) over median 6.4 years of follow-up.

Classes*	Model 2 HR (95% CI)	P value
Treated- no ARB	1 (Ref)	-
Treated- Any ARB	0.76 (0.63-0.91)	0.003
ARB Monotherapy	0.69 (0.52-0.90)	0.007
ARB plus other AHM(s)	0.80 (0.65-0.98)	0.03
Treated- no ACEI	1 (Ref)	-
Treated- Any ACEI	1.21 (1.01-1.46)	0.04
ACEi Monotherapy	1.29 (0.99-1.70)	0.06
ACEi plus other AHM(s)	1.17 (0.94-1.46)	0.16
Treated- no CCB	1 (Ref)	-
Treated- Any CCB	1.04 (0.87-1.26)	0.65
CCB Monotherapy	1.28 (0.90-1.82)	0.16
CCB plus other AHM(s)	1.00 (0.82-1.22)	0.99
Treated- no diuretic	1 (Ref)	-
Treated- Any diuretic	1.06 (0.88-1.29)	0.53
Diuretic Monotherapy	1.34 (0.88-2.05)	0.17
Diuretic plus other AHM(s)	1.03 (0.84-1.26)	0.79
Treated- no β-blocker	1 (Ref)	
Treated- Any β-blocker	0.92 (0.73-1.16)	0.48
β-blocker Monotherapy	1.01 (0.63-1.64)	0.95
β-blocker plus other AHM(s)	0.90 (0.71-1.16)	0.42



AHMs and blood pressure were treated as time-varying variables. The x-scale was on a log-scale.

*'Treated Any' includes the AHM as either monotherapy or combination therapy.