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Angiotensin II Receptor Blocker Therapy and Risk of Alzheimer's Disease and Related Dementias in Patients with Hypertension: A Large Claims-Based Cohort Study

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Abstract

Research on the potential protective benefits of angiotensin II receptor blockers (ARBs) in preventing Alzheimer's disease and related dementias (AD/ADRD) as well as cognitive impairment has produced mixed and inconclusive results. This retrospective cohort study utilized Optum's de-identified Clinformatics® Data Mart database and focused on hypertensive patients without any prior diagnosis of ADRD. Antihypertensive medication (AHM) categories were determined, and ARBs were further grouped according to their ability to cross the blood–brain barrier (BBB). Baseline patient characteristics were examined, while survival analyses relied on Kaplan–Meier (KM) survival curves together with multivariable-adjusted Cox proportional hazards (PH) models. The study population comprised 6,390,826 individuals diagnosed with hypertension, including 1,839,176 ARB users, 3,366,841 users of non-ARB antihypertensive agents, and 1,184,809 individuals not taking any AHM. Unadjusted KM curves showed a significantly lower cumulative incidence of ADRD among ARB users than among both other AHM users and non-users ($P < 0.0001$). Following adjustment in Cox PH models, ARB exposure was associated with a 20% reduction in the hazard of ADRD relative to angiotensin-converting enzyme inhibitor (ACEI) users, a 29% reduction compared with non-ARB/ACEI AHM users, and an 18% reduction versus AHM non-users (all $P < 0.0001$). Moreover, ARBs capable of crossing the BBB were linked to an 11% lower hazard than non-BBB-crossing ARBs, a 25% lower hazard than ARBs with undetermined permeability, and a 31% lower hazard than non-use of AHMs (all $P < 0.0001$).These findings indicate that, among patients with hypertension, ARBs provide superior protection against ADRD compared with ACEIs, other non-ARB/ACEI antihypertensive drugs, or the absence of antihypertensive treatment. Additionally, ARBs with enhanced BBB permeability were associated with a further reduction in ADRD risk. In view of the absence of effective curative therapies for AD, ADRD, or vascular dementia, the results highlight a valuable opportunity for prevention using widely available, cost-effective, and well-tolerated medications. Nevertheless, the constraints of administrative claims data must be acknowledged when considering these conclusions.

Keywords: ADRD, Antihypertensive medications, Hypertension, Blood–brain barrier, Dementia

Introduction

Hypertension (HTN) represents one of the leading chronic health conditions observed in older adults across the United States [1], influencing more than two-thirds of those aged 65 years or older [2]. Contemporary studies suggest that HTN constitutes a modifiable contributor to the development of Alzheimer's disease and related dementias (ADRD) as well as declines in cognitive function [3-8]. Accordingly, optimal management of HTN is increasingly regarded as an essential element in strategies aimed at lowering dementia risk [3-9]. This perspective has stimulated substantial interest in exploring how antihypertensive medications (AHMs) might influence susceptibility to ADRD.

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Investigations based on observational data examining the link between lowered blood pressure (BP) and reduced dementia risk have yielded divergent conclusions. A considerable number of such studies, including several meta-analyses, have identified a distinct advantage associated with AHM therapy in decreasing the likelihood of Alzheimer's disease (AD) or various forms of dementia [6, 7, 10-12]. In contrast, other analyses have reported no appreciable protective impact [13-15]. In parallel, multiple randomized controlled trials (RCTs) along with one non-randomized controlled trial have indicated that pharmacological reduction of elevated blood pressure via AHMs correlates with reduced incidence of AD and ADRD [11, 16-18].

Angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) function as primary therapeutic options for hypertension. These agents intervene in the renin-angiotensin system (RAS), with ARBs selectively blocking angiotensin II type-1 receptors (AT1Rs) and ACEIs inhibiting angiotensin-converting enzyme. Such actions effectively lower blood pressure while safeguarding cardiac and renal function [19, 20]. A meta-analysis synthesizing findings from 15 observational studies has pointed to possible neuroprotective properties of RAS-modulating drugs in the context of dementia prevention [21]. Although participant groups in that review presented with diverse comorbidities in addition to hypertension, the protective association emerged specifically for ARBs and not for ACEIs or other AHM categories, even though the medications share broadly comparable effects on blood pressure. This pattern is consistent with a growing collection of observational investigations that report lower risks of dementia and cognitive impairment among ARB users relative to those receiving ACEIs or other AHMs [22-26]. In contrast, findings from a randomized clinical trial assessing ARBs' ability to prevent or slow dementia progression and cognitive deterioration remained inconclusive [27]. To date, no prior research using large-scale electronic health records has specifically addressed the connection between ARB utilization and decreased dementia risk.

Leveraging extensive claims data, the current retrospective analysis sought to determine whether ARB use is associated with altered hazard rates for Alzheimer's disease and related dementias when compared with ACEI therapy, other classes of AHMs, and the absence of any AHM treatment among hypertensive individuals. The study further evaluated the relative effectiveness of ARBs versus ACEIs, additional antihypertensive therapies, or no medication in mitigating the risk of vascular dementia (VaD) in this population. Recognizing ongoing debate about the role of blood–brain barrier (BBB) permeability in amplifying the neuroprotective benefits of AHMs [28-31], the investigation also examined differences between BBB-penetrating ARBs and those that do not cross the BBB, ARBs with unclear permeability characteristics, and non-use of AHMs.

Materials and Methods

Study population

Data for this retrospective cohort study were obtained from Optum's de-identified Clinformatics® Data Mart (CDM) Database (version 1015), spanning the interval from January 1 2007 to October 15 2020. This resource consists of de-identified records drawn from a comprehensive adjudicated claims repository. Participants were required to have maintained continuous enrolment with at least twelve consecutive months of available claims information. The analytic cohort was restricted to patients who carried a hypertension diagnosis supported by inpatient or outpatient records and possessed at least one year of prescription history preceding the hypertension diagnosis date. Individuals were excluded if they had any documented ADRD diagnoses before the hypertension diagnosis, if they recorded only a single medical encounter during the enrolment window, or if they lacked essential diagnostic, procedural, laboratory, or demographic data before the index date (defined as the date of hypertension diagnosis). Application of these criteria resulted in a final sample of 6,390,826 unique patients.

Identification of hypertension and alzheimer's disease and related dementias

Diagnoses were ascertained using the World Health Organization (WHO) International Classification of Diseases, Ninth Revision (ICD-9) [32], Tenth Revision (ICD-10) [33], and the Anatomical Therapeutic Chemical (ATC) classification system maintained by the WHO Collaborating Center for Drug Statistics Methodology (WHOCC) [34]. Incident Alzheimer's disease and related dementias were identified based on either: (1) the initial diagnosis date for vascular dementia (ICD-9: 290.4; ICD-10: F01.5), non-specific dementia (ICD-9: 290.0, 290.1, 290.2, 290.3, 290.8, 290.9, 797.0;

ICD-10: F02.8, F03.9, F04, F05, F06.0, F06.1, F06.2, F06.3, R41.81), Lewy-body associated dementia (ICD-9: 331.82; ICD-10: G31.83), frontotemporal dementia (ICD-9: 331.1; ICD-10: G31.0), or Alzheimer's disease (ICD-9: 331.0; ICD-10: G30.0, G30.1, G30.8, G30.9) [35], or (2) the occurrence of a second pharmacy claim for anti-dementia agents (ATC: N06D) within any six-month interval throughout the enrolment period [34]. Hypertension status required documentation of at least two separate hypertension diagnosis codes (ICD-9: 362.11, 401.x, 402.x, 403.x, 404.x, 405.x, 437.2, 496; ICD-10: H35.03x, I10, I11.x, I12.x, I13.x, I15.x, I67.4, N26.2) recorded on different dates within a 24-month timeframe [36].

Classification of antihypertensive medications

We defined use of antihypertensive medications as filling two or more prescriptions for such agents on distinct dates within any given 12-month interval. Assignment of specific AHM agents to therapeutic classes was performed with reference to the WHOCC ATC classification system [34] and informed by expert clinical review. Five principal AHM groups were delineated: diuretics (ATC: C03), beta blockers (BB; ATC: C07), calcium channel blockers (CCBs, both long-acting and short-acting forms; ATC: C08), angiotensin-converting enzyme inhibitors (ACEIs; ATC: C09A, C09B), and angiotensin II receptor blockers (ARBs; ATC: C09C, C09D). Agents prescribed less often, such as renin inhibitors and hydralazine, were placed in a residual 'Other' group (ATC: C02). Each therapeutic class encompassed both monotherapy and fixed-dose combination products (for instance, the metoprolol/hydrochlorothiazide combination was allocated to the beta blockers group) following the WHOCC ATC conventions. These ATC-designated drugs were then matched to generic names available in the CDM dataset.

For the survival analyses, the identified AHM groups were consolidated into three analytic categories: ARBs, ACEIs, and all other AHMs (diuretics, beta blockers, calcium channel blockers, and the residual group). Medication dosage data were not considered in this investigation.

ARBs were further subdivided according to blood–brain barrier (BBB) permeability into BBB-crossing ARBs, non-BBB-crossing ARBs, and those with undetermined BBB permeability. This categorization followed the framework developed by Ho *et al.* [28] and is summarised in **Table 1**.

Table 1. Categorization of angiotensin II receptor blockers based on blood–brain barrier permeability.

Blood–Brain Barrier (BBB)-Crossing ARBs	Non-BBB-Crossing ARBs	Undetermined (Not Analyzed)
Telmisartan	Olmesartan	Valsartan
Candesartan	Eprosartan	Azilsartan
	Irbesartan	
	Losartan	

Confounding factors

Confounders associated with Alzheimer's disease and related dementias were derived from those reported by Bukhbinder *et al.* [36] and refined through application of a modified disjunctive cause selection approach [37]. Acute myocardial infarction (AMI) was deliberately excluded from the final list owing to its direct causal link to ischemic heart disease. The retained confounders encompassed: (1) demographic variables—age divided into six bands (< 65, 65–69, 70–74, 75–79, 80–84, 85–90), with a maximum recorded age of 90 years in the CDM database, and self-reported sex; (2) presence of specified comorbidities—atrial fibrillation (AF), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), hyperlipidaemia (HL), ischemic heart disease (IHD), obesity, traumatic brain injury (TBI), type II diabetes mellitus (T2DM), stroke, anxiety disorder, depression, alcohol use disorder, substance use disorder, and tobacco use disorder; and (3) exposure to particular pharmacotherapies—statins and metformin. No missing values existed for demographics, comorbidities, or medication use within the study cohort. Comorbid conditions were primarily identified via ICD codes, supplemented by Current Procedural Terminology (CPT) codes and Healthcare Common Procedure Coding System (HCPCS) codes for tobacco use disorder. Identification of statin and metformin use relied exclusively on ATC codes, irrespective of dosage.

The Cox proportional hazards model assumptions were evaluated using Schoenfeld residuals, and no violations were observed among the included confounders. Because race data were unavailable in the CDM database, sensitivity analyses exploring the potential influence of race were performed using the E-value method [38].

Study design

To assess how ARB therapy relates to the onset and course of ADRD in comparison with alternative antihypertensive regimens, the eligible population was limited to individuals with hypertension who had no history of ADRD. This decision was informed by prior research showing only modest effects of AHMs on ADRD development among people with normal blood pressure [10, 39]. Including normotensive subjects would also have complicated adjustment for hypertension itself, since AHM prescriptions are uncommon in the absence of elevated blood pressure.

The index date was set as the day of the first recorded hypertension diagnosis. Time at risk was measured from this index date until either (1) the initial diagnosis of ADRD for patients who developed the outcome, or (2) the date of the last recorded healthcare contact for those who did not. Healthcare contacts included all inpatient admissions and outpatient visits with relevant ICD codes, regardless of duration.

Exposure to antihypertensive medications was defined in the following manner: 'AHM users' included all patients prescribed at least one such agent, while 'AHM non-users' included those without any AHM prescriptions. Throughout the analyses, 'ARB users' consisted of individuals prescribed ARBs, whether as monotherapy or in combination regimens. Within **Table 2**, 'non-ARB AHM users' referred to patients receiving at least one AHM excluding any ARBs. For the survival models displayed in **Table 3**, 'ACEI users' described patients treated with ACEIs (alone or combined) but without any ARBs. 'Other AHM users' denoted patients prescribed antihypertensive agents other than ARBs or ACEIs. A separate subgroup analysis restricted to monotherapy recipients defined 'ARB only users' as those taking ARBs exclusively and 'ARB only non-users' as those taking a single AHM from any non-ARB class.

Table 2. Baseline demographic and clinical characteristics among 6,390,826 hypertensive patients, stratified according to antihypertensive medication exposure.[a,b]

Characteristic	P-value	AHM Non-Users (N = 1,184,809)	Non-ARB Antihypertensive Medication (AHM) Users (N = 3,366,841)	ARB Users (N = 1,839,176)
Sex				
Female	< 0.0001	602,390 (50.84%)	1,733,084 (51.48%)	1,021,499 (55.54%)
Male	—	582,419 (49.16%)	1,633,757 (48.52%)	817,677 (44.46%)
Age at initial hypertension diagnosis, years (mean ± SD)	< 0.0001	65.27 ± 11.20	63.76 ± 10.93	63.67 ± 10.64
New ADRD diagnosis	< 0.0001	97,217 (8.21%)	359,782 (10.69%)	180,137 (9.79%)
Interval from hypertension diagnosis to ADRD diagnosis, months (mean ± SD)	< 0.0001	40.56 ± 34.70	47.62 ± 39.65	57.96 ± 41.96
Follow-up duration without ADRD after hypertension diagnosis, months (mean ± SD)	< 0.0001	49.93 ± 36.14	64.84 ± 38.94	74.98 ± 40.28
New vascular dementia (VaD) diagnosis	< 0.0001	7064 (0.60%)	30,792 (0.91%)	15,060 (0.82%)
Interval from hypertension diagnosis to VaD diagnosis, months (mean ± SD)	< 0.0001	37.83 ± 33.02	44.12 ± 37.31	55.80 ± 40.66
Follow-up duration without VaD after hypertension diagnosis, months (mean ± SD)	< 0.0001	51.22 ± 36.28	66.19 ± 39.10	76.26 ± 40.41
Atrial fibrillation (AF)	< 0.0001	160,756 (13.57%)	621,777 (18.47%)	349,803 (19.02%)
Congestive heart failure (CHF)	< 0.0001	153,309 (12.94%)	709,419 (21.07%)	452,375 (24.60%)
Chronic obstructive pulmonary disease (COPD)	< 0.0001	222,121 (18.75%)	802,033 (23.82%)	452,205 (24.59%)
Hyperlipidaemia	< 0.0001	953,746 (80.50%)	2,870,737 (85.27%)	1,654,191 (89.94%)

Ischaemic heart disease (IHD)	< 0.0001	325,028 (27.43%)	1,253,834 (37.24%)	756,698 (41.14%)
Obesity	< 0.0001	305,310 (25.77%)	1,159,778 (34.45%)	781,029 (42.47%)
Stroke history	< 0.0001	112,011 (9.45%)	431,573 (12.82%)	250,576 (13.62%)
Traumatic brain injury (TBI)	< 0.0001	138,821 (11.72%)	450,283 (13.37%)	249,911 (13.59%)
Type 2 diabetes mellitus (T2DM)	< 0.0001	272,708 (23.02%)	1,168,933 (34.72%)	789,539 (42.93%)
Anxiety disorder	< 0.0001	159,800 (13.49%)	507,022 (15.06%)	279,828 (15.21%)
Depressive disorder	< 0.0001	169,786 (14.33%)	587,343 (17.44%)	316,856 (17.23%)
Substance use disorder	< 0.0001	159,470 (13.46%)	619,321 (18.39%)	286,998 (15.60%)
Alcohol use disorder	< 0.0001	48,208 (4.07%)	185,524 (5.51%)	84,431 (4.59%)
Tobacco use disorder	< 0.0001	375,789 (31.72%)	1,195,815 (35.52%)	616,680 (33.53%)
Metformin therapy	< 0.0001	49,002 (4.14%)	635,579 (18.88%)	437,895 (23.81%)
Statin therapy	< 0.0001	227,425 (19.20%)	1,846,215 (54.84%)	1,093,788 (59.47%)

Note: P-values were derived from the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables.
ARB users: patients receiving at least one ARB; Non-ARB AHM users: patients receiving at least one antihypertensive medication other than ARBs; AHM non-users: patients receiving none of the identified antihypertensive medications.

a Data are presented as mean (SD) for continuous variables or number (%) for categorical variables.
b No data were missing.
c Median (IQR): ARB users 50.80 (22.83, 90.10), Non-ARB AHM users 38.83 (13.93, 74.07), AHM non-users 33.83 (11.17, 60.80).
d Median (IQR): ARB users 67.17 (44.77, 101.97), Non-ARB AHM users 56.33 (37.33, 87.47), AHM non-users 45.03 (22.43, 69.57).
e Median (IQR): ARB users 48.57 (22.40, 84.03), Non-ARB AHM users 36.10 (12.87, 66.77), AHM non-users 31.12 (10.13, 57.14).
f Median (IQR): ARB users 68.79 (45.52, 104.59), Non-ARB AHM users 46.26 (24.02, 70.96), AHM non-users 46.26 (24.02, 70.96).

Table 3. Adjusted Cox proportional hazards models for the association between ARB exposure and risk of ADRD or vascular dementia, relative to ACEI therapy, other AHM use, and non-use of AHMs within the CDM database.[a]

Comparison	**Vascular Dementia (VaD)**		**Alzheimer's Disease and Related Dementias (ADRD)**	
	P-value	**Adjusted HR (95% CI)**	**P-value**	**Adjusted HR (95% CI)**
ARB users vs. ACEI users	< 0.0001	0.77 (0.76, 0.79)	< 0.0001	0.80 (0.79, 0.80)
ARB users vs. non-ARB antihypertensive medication (AHM) users	< 0.0001	0.75 (0.73, 0.77)	< 0.0001	0.71 (0.70, 0.71)
ARB users vs. antihypertensive medication (AHM) non-users	< 0.0001	0.82 (0.79, 0.85)	< 0.0001	0.82 (0.81, 0.83)

ARB users: patients receiving at least one ARB; ACEI users: patients receiving at least one ACEI without concurrent ARB use; Other AHM users: patients receiving at least one antihypertensive medication other than ARBs or ACEIs; AHM non-users: patients receiving none of the identified antihypertensive medications.
Abbreviations: AHM, antihypertensive medication; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; aHR, adjusted hazard ratio.

[a] Hazard ratios were adjusted for age (<65, 65–69, 70–74, 75–79, 80–84, 85–90), sex, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, hyperlipidaemia, ischemic heart disease, obesity, traumatic brain injury, type II diabetes, stroke, anxiety disorder, depression, substance use disorder, alcohol use disorder, tobacco use, and exposure to metformin and statins.

[b] ARB users versus ACEI users: Total 1,839,176 versus 2,220,709; ADRD (event %) 180,137 (9.79%) versus 237,887 (10.71%); ADRD total person-years 134,832,348 versus 146,767,786; ADRD rates per 1000 person-years 1.336 versus 1.621; VaD 15,060 versus 21,368; VaD total person-years 139,940,164 versus 153,468,054; VaD rates per 1000 person-years 0.108 versus 0.139.

[c] ARB users versus Other AHM users: Total 1,839,176 versus 1,146,132; ADRD (event %) 180,137 (9.79%) versus 121,895 (10.64%); ADRD total person-years 134,832,348 versus 65,357,919; ADRD rates per 1000 person-years 1.336 versus 1.865; VaD 15,060 versus 9424; VaD total person-years 139,940,164 versus 68,715,670; VaD rates per 1000 person-years 0.108 versus 0.137.

[d] ARB users versus AHM non-users: Total 1,839,176 versus 1,184,809; ADRD (event %) 180,137 (9.79%) versus 97,217 (8.21%); ADRD total person-years 134,832,348 versus 58,244,854; ADRD rates per 1000 person-years 1.336 versus 1.669; VaD 15,060 versus 7064; VaD total person-years 139,940,164 versus 60,592,308; VaD rates per 1000 person-years 0.108 versus 0.117.

Ethics

This investigation was evaluated and approved by the Institutional Review Board of the University of Texas Health Science Center, identified by IRB Number 'HSC-SBMI-21-0965' and titled 'Deep learning and knowledge graph on EHR for clinical decision support, risk prediction, and drug-repurposing'. Because the analysis relied on retrospective claims data, participant consent was waived.

Statistics

Group differences in baseline characteristics were evaluated with the Chi-square test for categorical data and the Kruskal–Wallis test for continuous variables. Baseline features were summarized using frequencies and percentages (%) for categorical measures and means with standard deviations (SD) for continuous measures. Follow-up duration was additionally described by the median and interquartile range (IQR). The Chi-square and Kruskal–Wallis tests were further applied to explore independent relationships between ADRD diagnostic status and AHM use.

A Cox proportional hazards (PH) model was fitted to assess the relationship between AHM exposure and the interval from MCI to ADRD, accounting for the previously identified confounders. The validity of the proportional hazards assumption was inspected visually via Kaplan–Meier curves and log(−log) plots [40]. Potential breaches of this assumption were also examined through a statistical test relying on scaled Schoenfeld residuals [41]. Because no violation was detected, we used the standard log-rank test.

All statistical computations were executed in RStudio with R version 4.1.2. Statistical significance was determined at a two-tailed P-value of ≤ 0.05.

Role of funders

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Results and Discussion

Baseline patient characteristics

The CDM repository included 6,572,172 individuals with hypertension. Application of the predefined inclusion and exclusion criteria yielded a final analytic sample of 6,390,826 distinct patients with hypertension (**Figure 1**). Within this cohort, 1,839,176 individuals were prescribed ARBs, 3,366,841 received AHMs excluding ARBs, and 1,184,809 did not receive any AHMs. As summarized in **Table 2**, females constituted more than half of the ARB group (55.54%), representing a significantly larger share than among non-ARB AHM recipients or those without AHM exposure ($P < 0.0001$). The average age at initial hypertension diagnosis was 63.67 years among ARB users and 63.76 years among non-ARB AHM users—both nearly two years younger than the 65.27 years recorded for AHM non-users ($P < 0.0001$). For patients who progressed to ADRD, the average duration from hypertension diagnosis to ADRD onset was greatest in the ARB group (57.96 months), intermediate in non-ARB AHM users (47.62 months), and shortest among non-users (40.56 months). Individuals not using AHMs displayed markedly lower prevalence of all examined comorbidities (all $P < 0.0001$) and decreased utilization of metformin and statins (both $P < 0.0001$) in comparison with both ARB and non-ARB AHM groups.

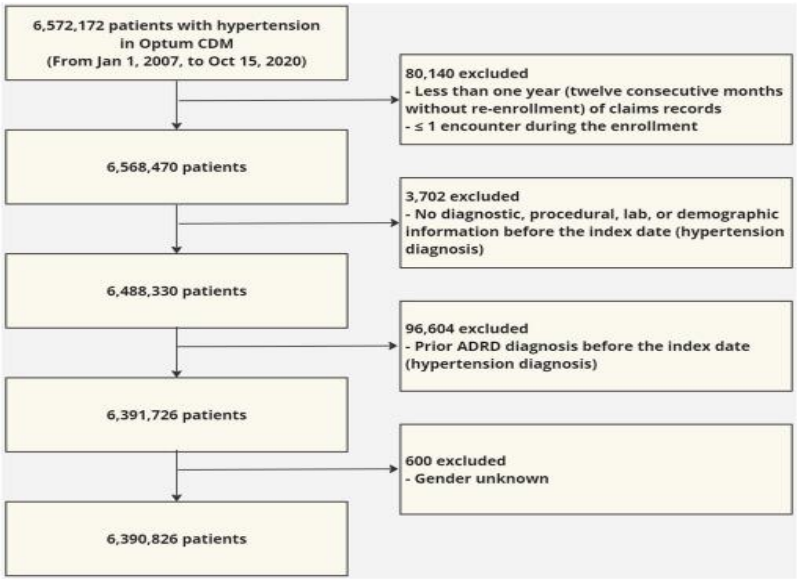

Figure 1. Patient selection flowchart showing the final cohort after implementation of inclusion and exclusion criteria.

Survival analyses

Kaplan–meier survival curves

Figure 2 presents unadjusted Kaplan–Meier curves illustrating cumulative ADRD hazards in hypertensive patients across categories of AHM exposure: ARBs, ACEIs, other AHMs, and no AHMs. ARB-treated patients exhibited persistently lower cumulative hazards than those prescribed other AHMs or those without AHM therapy ($P < 0.0001$). ACEI users displayed higher cumulative hazards than ARB users yet lower hazards than recipients of other AHMs. Hypertensive individuals using AHMs excluding ARBs and ACEIs showed elevated cumulative hazards compared with patients not receiving any antihypertensive medication.

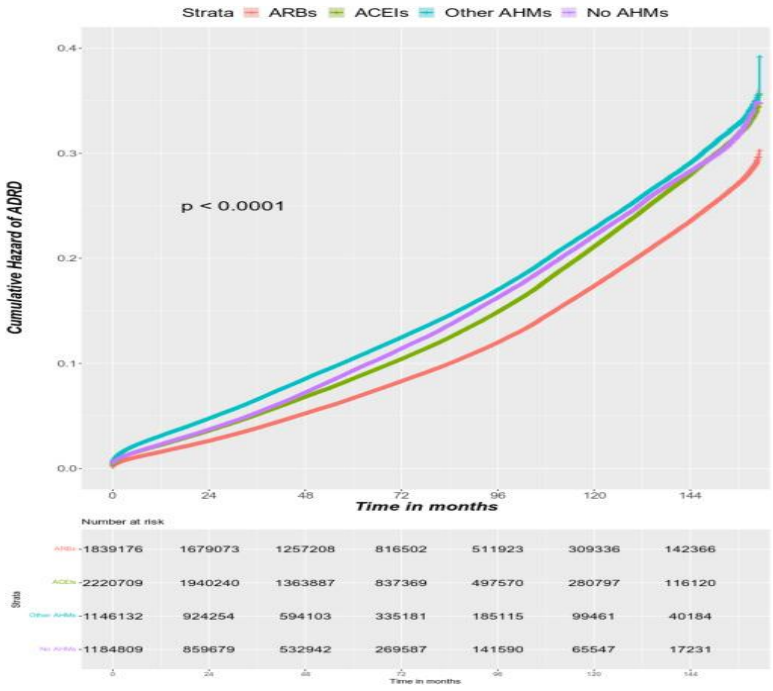

Figure 2. Kaplan–Meier plot of cumulative ADRD hazards among hypertensive patients by AHM category: ARBs, ACEIs, other AHMs, and no AHMs. Strata are indicated by color: ARBs (red), ACEIs (green), Other

AHMs (blue), and no AHMs (purple). P-values are derived from comparisons of Kaplan–Meier estimates between strata. The Y-axis denotes cumulative hazard of ADRD (scale: 0.0 to 0.4). The X-axis represents time in months (labeled every 24 months, range: 0 to 144). The plot incorporates a risk table below the curves indicating the number at risk at 24-month intervals for each group.

Cox proportional hazards modeling in the CDM data revealed that ARB users had a 20% decreased risk of incident ADRD relative to ACEI users (aHR (95% CI): 0.80 (0.79, 0.80); P < 0.0001) following adjustment for relevant confounders. ARB exposure was also associated with a 29% reduction in ADRD risk compared with use of AHMs other than ARBs or ACEIs (aHR (95% CI): 0.71 (0.70, 0.71); P < 0.0001). When benchmarked against patients without any AHM treatment, ARB use correlated with significantly lower ADRD incidence after hypertension diagnosis (aHR (95% CI): 0.82 (0.81, 0.83); P < 0.0001). Further details of the Cox proportional hazards findings appear in **Table 3**.

Parallel Cox proportional hazards analyses using vascular dementia as the primary endpoint were likewise performed (**Table 3**). ARB therapy correlated with substantially diminished hazards of ADRD development in comparison with ACEI use, other AHM use, and non-use of AHMs (all P < 0.0001). In particular, ARB users experienced a 23% lower hazard of vascular dementia than ACEI users (aHR (95% CI): 0.77 (0.76, 0.79)) and a 25% lower hazard than users of AHMs excluding ARBs and ACEIs (aHR (95% CI): 0.75 (0.73, 0.77)). Relative to complete non-use of AHMs, ARB exposure was associated with an 18% reduction in vascular dementia risk (aHR (95% CI): 0.82 (0.79, 0.85)).

Additional survival analyses within the CDM dataset evaluated ADRD and vascular dementia risks for users of the five primary AHM classes (ARBs, ACEIs, CCBs, Diuretics, Beta Blockers) against both non-users of the corresponding agent and non-users of all AHMs. Subgroup evaluations focused on patients receiving monotherapy with a single AHM, comparing risks to non-users of that specific medication and to those avoiding all AHMs.

The adjusted hazard of ADRD was additionally assessed among ARB users according to blood–brain barrier (BBB) crossing capability. Treatment with BBB-permeable ARBs was associated with an 11% and 25% reduction in ADRD hazard compared with non-permeable ARBs and ARBs of indeterminate permeability, respectively (both P < 0.0001). Furthermore, BBB-crossing ARBs conferred a 31% lower adjusted hazard of ADRD relative to the absence of any AHM therapy (aHR (95% CI): 0.69 (0.67, 0.70); P < 0.0001). Complete Cox proportional hazards results for these comparisons are detailed in **Table 4**.

Table 4. Cox proportional hazards analysis of BBB-crossing ARB consumption in relation to ADRD or vascular dementia development, relative to non-BBB-crossing ARBs, undetermined ARBs, and non-use of AHMs in the CDM dataset.a

Comparison	Vascular Dementia (VaD)		Alzheimer's Disease and Related Dementias (ADRD)	
	P-value	Adjusted HR (95% CI)	P-value	Adjusted HR (95% CI)
BBB-crossing ARB users vs. non-BBB-crossing ARB users	0.07	0.94 (0.88, 1.01)	<0.0001	0.89 (0.88, 0.91)
BBB-crossing ARB users vs. undetermined ARB users	<0.0001	0.77 (0.71, 0.83)	<0.0001	0.75 (0.73, 0.77)
BBB-crossing ARB users vs. antihypertensive medication (AHM) non-users	<0.0001	0.78 (0.71, 0.84)	<0.0001	0.69 (0.67, 0.70)

BBB-ARB users: individuals prescribed at least one BBB-crossing ARB; Non-BBB ARB users: individuals prescribed at least one non-BBB-crossing ARB without any BBB-crossing ARB exposure; Undetermined ARB users: individuals prescribed at least one ARB of undetermined BBB status without exposure to BBB-crossing or non-BBB-crossing ARBs; AHM non-users: individuals receiving none of the studied antihypertensive medications.

Abbreviations: AHM, antihypertensive medication; BBB, blood–brain barrier; ARB, angiotensin II receptor blocker; CI, confidence interval; aHR, adjusted hazard ratio.

[a] Hazard ratios were adjusted for age, sex, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, hyperlipidemia, ischemic heart disease, obesity, traumatic brain injury, type II diabetes, stroke, anxiety disorder, depression, substance use disorder, alcohol use disorder, tobacco use, and use of metformin and statins.

[b] BBB-ARBs users versus Non-BBB-ARBs users: Total 126,509 versus 1,436,855; ADRD (event %) 10,635 (8.41%) versus 139,165 (9.69%); ADRD total person-years 10,224,501 versus 105,744,332; ADRD rates per 1000 person-years 1.040 versus 1.316; VaD 916 versus 11,403; VaD total person-years 10,540,287 versus 109,683,456; VaD rates per 1000 person-years 0.087 versus 0.104.

[c] BBB-ARBs users versus Undetermined ARBs users: Total 126,509 versus 268,816; ADRD (event %) 10,635 (8.41%) versus 29,612 (11.02%); ADRD total person-years 10,224,501 versus 18,352,429; ADRD rates per 1000 person-years 1.040 versus 1.614; VaD 916 versus 2660; VaD total person-years 10,540,287 versus 19,184,695; VaD rates per 1000 person-years 0.087 versus 0.139.

[d] BBB-ARBs users versus AHM non-users: Total 126,509 versus 1,184,809; ADRD (event %) 10,635 (8.41%) versus 97,217 (8.21%); ADRD total person-years 10,224,501 versus 58,244,854; ADRD rates per 1000 person-years 1.040 versus 1.669; VaD 916 versus 7064; VaD total person-years 10,540,287 versus 60,592,308; VaD rates per 1000 person-years 0.087 versus 0.117.

Regarding vascular dementia, BBB-crossing ARB users did not exhibit a statistically significant hazard reduction compared with non-BBB-crossing ARB users (aHR (95% CI): 0.94 (0.88, 1.01); P = 0.0700). However, BBB-crossing ARB therapy was linked to a 23% lower adjusted hazard of vascular dementia relative to undetermined ARBs (aHR (95% CI): 0.77 (0.71, 0.83); P < 0.0001). BBB-crossing ARB use was further associated with a 22% reduction in vascular dementia risk compared with no AHM exposure (aHR (95% CI): 0.78 (0.71, 0.84); P < 0.0001).

According to current evidence, prior research has not explored whether angiotensin II receptor blocker intake correlates with a decreased risk of Alzheimer's disease and related dementias or vascular dementia, particularly when leveraging extensive electronic health record datasets such as the Common Data Model. The present analysis indicates that angiotensin II receptor blocker therapy is linked to a lower rate of new cases of Alzheimer's disease and related dementias as well as vascular dementia, in comparison with angiotensin-converting enzyme inhibitor therapy, other types of antihypertensive medications (excluding ARBs and ACEIs), and the complete absence of antihypertensive treatment. With a robust cohort exceeding 6 million individuals, this investigation provides strong empirical backing for the reliability of these results.

Importance of the findings

No effective cure is currently available for Alzheimer's disease, Alzheimer's disease and related dementias, or vascular dementia. Prevention therefore remains essential. Identifying ARBs as a treatment associated with substantially reduced hazard ratios for both ADRD and VaD onset is clinically relevant, as it offers a preventive strategy that is affordable and simple to implement in patients already managed for hypertension. While confirmation through additional research using varied methodologies is necessary, the lack of any documented safety concerns when substituting ARBs for ACEIs in hypertensive individuals supports the feasibility of adopting such prescribing shifts in the interim.

Relation to earlier research

The observation that ARBs provide greater protection than ACEIs against the onset of ADRD in hypertensive populations is consistent with findings from several earlier observational investigations, which reported lower risks of dementia and cognitive deterioration with ARBs compared to ACEIs [22-26]. Both drug classes inhibit the renin–angiotensin system and reduce the activity of angiotensin II at type-1 receptors. Beyond minor differences in tolerability and applicability in certain situations, no substantial therapeutic superiority has been established between them, so current guidelines endorse them as equivalent options [42]. In clinical settings, ACEIs are more frequently chosen because of lower costs, while ARBs are generally reserved for patients who are intolerant of ACEIs [43].

No previous work, to our knowledge, has evaluated ADRD incidence among ARB users relative to individuals receiving other antihypertensive agents besides ACEIs. Similarly, comparisons of ADRD hazard in hypertensive ARB users versus those not receiving any antihypertensive therapy appear absent from the literature.

Multiple studies with analogous participant groups and outcome definitions have yielded results that support the current observations. One large retrospective cohort involving 1,343,334 Medicare enrollees found that ARB users of both sexes showed odds ratios of 0.834 (males) and 0.941 (females) for developing Alzheimer's disease compared with users of non-RAS antihypertensive medications [44]. Another retrospective analysis of 403 patients with hypertension and baseline mild cognitive impairment linked ARB treatment to a 55% decreased risk of progressing to dementia versus ACEIs, a 51% reduction versus other primary antihypertensive classes, and a 69% reduction versus no antihypertensive use [26]. A prospective cohort of 819,491 mostly male cardiovascular disease patients reported hazard ratios for new-onset dementia of 0.76 for the ARB group versus other cardiovascular drugs and 0.81 versus lisinopril [25].

Because these claims-based results on reduced ADRD risk among ARB users (relative to ACEI users, other antihypertensive users, or non-users) derive from a hypertensive population, they should be interpreted cautiously alongside community-based cohorts or studies involving healthy participants or individuals with alternative comorbidities. Outcome definitions also vary across investigations. Therefore, prospective cohort studies and, ideally, randomized controlled trials across heterogeneous populations with harmonized baseline and endpoint criteria are needed to validate these observations.

Potential underlying mechanisms

The differing associations of ARBs and ACEIs with ADRD risk may arise from their distinct modes of action: ARBs selectively block angiotensin II from interacting with AT1 receptors, thereby preventing its signaling, while ACEIs reduce angiotensin II production by inhibiting the enzyme responsible for converting angiotensin I to its active form [19, 20]. Rigorous testing of whether ARBs afford superior neuroprotection, through approaches such as large-scale emulated trials and randomized controlled studies, is warranted. Further pharmacological research examining potential cognitive advantages of both antihypertensive categories would also be valuable.

Angiotensin-converting enzyme is known to break down amyloid β (Aβ) protein [45, 46], a central element in Alzheimer's disease pathology [47]. However, the extent to which this process relates to the observed findings remains unclear.

Vascular dementia

Following Alzheimer's disease, vascular dementia represents one of the leading causes of dementia, responsible for roughly 15% of cases. Although vascular and Alzheimer-type degenerative changes frequently coexist, a precise mechanistic connection between them has not been definitively identified [48]. This study found that ARB use correlated with a decreased hazard of vascular dementia compared with ACEI use, other antihypertensive medications, or no antihypertensive treatment. ARB users experienced a 23% reduction in vascular dementia hazard (adjusted hazard ratio [95% CI]: 0.77 [0.76, 0.79]) relative to ACEI users. These results suggest that ARB benefits may involve mechanisms beyond blood pressure control and general vascular protection, potentially including direct effects on brain function. Although the analysis did not compare the relative strength of protection against VaD versus ADRD, it confirmed that ARBs effectively lower the hazard for both disorders.

Penetration of the blood–brain barrier

Renin–angiotensin system medications that can traverse the blood–brain barrier may exert cognitive effects through both vascular and neuronal pathways [49]. We therefore subdivided ARBs into those that cross the blood–brain barrier, those that do not, and those with undetermined status, then assessed differences in ADRD and vascular dementia hazards across these subgroups. The analysis revealed that BBB-crossing ARBs were associated with a lower ADRD hazard than non-crossing ARBs, whereas no significant difference emerged for vascular dementia risk between these categories. Although limited prior research has suggested cognitive advantages for BBB-crossing ARBs [28, 50], further work is needed to clarify the connection between blood–brain barrier permeability and potential neuroprotective properties.

Limitations

This investigation has several limitations. The analysis relies on the assumption that the claims data and corresponding ICD codes are sufficiently accurate; however, this assumption cannot be independently confirmed or thoroughly examined within the scope of the present study. In addition, hazard ratios derived from

the retrospective design may be susceptible to inherent selection bias, given that hazard ratios can vary over time. To address this, we presented Kaplan–Meier survival curves and survival-time distributions for individuals with and without ADRD or VaD, offering insight into temporal patterns. Because the cohort includes patients with hypertension who did not receive any antihypertensive medication (AHM non-users), the index date was defined as the date of hypertension diagnosis rather than the initiation of antihypertensive treatment. This approach may introduce immortal time bias.

Furthermore, although prescription records are available, they do not necessarily reflect actual medication intake, as patient adherence could not be evaluated. Assuming full adherence in the analysis means that any real-world non-adherence would bias results toward the null. Moreover, the data do not account for dosage or duration of AHM use, limiting the ability to detect dose- or time-dependent effects on ADRD risk. Future research incorporating such details would provide greater clarity regarding the effectiveness of AHMs in mitigating ADRD risk.

Because of the characteristics of claims data, diagnoses such as ADRD and hypertension are not consistently verified by the same clinicians across patients, and follow-up information may be incomplete if individuals discontinue insurance coverage. In this Common Data Model database, the absence of claims for a specific diagnosis is interpreted as the absence of that condition, which may misclassify missing data. Loss to follow-up may also be influenced by the unavailability of information on insurance subscription status (active or inactive). The insurance claim date was taken as the date of physician diagnosis. At the same time, this does not affect Cox proportional hazards results; it could influence Kaplan–Meier estimates if there are minor delays between claim and diagnosis dates. Additionally, the database lacks mortality information (such as death status or date), preventing evaluation of death as a competing risk. Given these constraints inherent to retrospective analyses of claims data, interpret the findings within their appropriate context, and consider corroboration through complementary study designs.

Methodological challenges related to confounding may arise from using claims data. For example, race was not recorded in the CDM database and thus represents a potential unmeasured confounder. Sensitivity analyses using the E-value were therefore conducted for race, yielding values ranging from 1.74 to 2.17 for ADRD or VaD outcomes when comparing ARB users with ACEI users, other AHM users, or AHM non-users. These figures indicate that only modest unmeasured confounding would be required to nullify the observed associations. Other potential confounders relevant to ADRD in hypertensive patients, such as hypoacusis [51] and obstructive sleep apnoea [52], could not be included because data were unavailable, which may have introduced bias. Adjusting for confounders measured after the index date risks collider stratification bias or misclassifying mediators as confounders [53]. Residual confounding may also result from categorizing age or measurement error in variables such as tobacco use. Recall bias is probable for self-reported behaviors including tobacco, substance, or alcohol use due to underreporting. When comparing ADRD hazards between ARB users and AHM non-users, confounding by indication warrants attention, as AHM non-users exhibited lower comorbidity prevalence, potentially reflecting better overall health or reduced engagement with medical care.

Nevertheless, the reported hazard ratios and person-year rates demonstrate that AHM non-users experienced a significantly higher ADRD hazard than ARB users despite such potential biases. Genetic factors were unavailable in the dataset, despite the established role of variants such as the apolipoprotein E (APOE) genotype as risk factors for dementia, Alzheimer's disease, and cardiovascular disease [54]. Social determinants of health, including socioeconomic status and healthcare access, are similarly absent from claims data and may influence ADRD incidence and progression. For instance, the higher cost of ARBs relative to ACEIs (though this gap is narrowing) could mean that ARB users tend to have greater socioeconomic resources, which might affect ADRD risk. Future studies might benefit from imputing social determinants using proxies such as zip code data. Finally, temporal changes in prescribing patterns and AHM utilization during the study period (January 1, 2007, to October 15, 2020) were not adjusted for and could influence ADRD outcomes. Consequently, the reported associations should be viewed cautiously, and these limitations should inform the design of replication studies, including randomized controlled trials and prospective cohorts.

Conclusion

In summary, this study showed that ARB use was associated with a significantly lower hazard of ADRD than ACEI use, other antihypertensive medications, or no antihypertensive medication use among patients with hypertension in a large claims-based dataset. Comparable protective associations were observed for vascular dementia. Among ARB users, those prescribed BBB-crossing ARBs exhibited reduced hazards of both ADRD and vascular dementia relative to users of non-BBB-crossing ARBs, ARBs of undetermined BBB status, and non-users of antihypertensive medications. These findings highlight promising opportunities for drug repurposing strategies aimed at dementia prevention and encourage further evaluation through diverse research designs, including randomized controlled trials.

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References

1. NCOAging. Top 10 chronic conditions affecting older adults. https://ncoa.org/article/the-top-10-most-common-chronic-conditions-in-older-adults (n.d.). Accessed 10 Aug 2023.
2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.
3. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023;19(4):1598-695.
4. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA Neurol. 2017;74(10):1246-54.
5. Rönnemaa E, Zethelius B, Lannfelt L, Kilander L. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. Dement Geriatr Cogn Disord. 2011;31(6):460-6.
6. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. Hypertension. 2016;68(6):e67-94.
7. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-46.
8. Omura JD, McGuire LC, Patel R, Baumgart M, Lamb R, Jeffers EM, et al. Modifiable risk factors for Alzheimer disease and related dementias among adults aged ≥45 Years - United States, 2019. MMWR Morb Mortal Wkly Rep. 2022;71(20):680-5.
9. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Preventing Dementia and Cognitive Impairment. In: Downey A, Stroud C, Landis S, Leshner AI, editors. Preventing cognitive decline and dementia: a way forward. Washington (DC): National Academies Press (US); 2017.
10. Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Khalife C, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. Lancet Neurol. 2020;19(1):61-70.
11. Rouch L, Cestac P, Hanon O, Cool C, Helmer C, Bouhanick B, et al. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. CNS Drugs. 2015;29(2):113-30.
12. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens. 2013;31(6):1073-82.
13. Peters R, Yasar S, Anderson CS, Andrews S, Antikainen R, Arima H, et al. Investigation of antihypertensive class, dementia, and cognitive

decline: a meta-analysis. Neurology. 2020;94(3):e267-81.
14. Gelber RP, Ross GW, Petrovitch H, Masaki KH, Launer LJ, White LR. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. Neurology. 2013;81(10):888-95.
15. Xu G, Bai F, Lin X, Wang Q, Wu Q, Sun S, et al. Association between antihypertensive drug use and the incidence of cognitive decline and dementia: a meta-analysis of prospective cohort studies. Biomed Res Int. 2017;2017:4368474.
16. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA. 2019;321(6):553-61.
17. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7(8):683-9.
18. Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet. 2016;388(10046):797-805.
19. Barreras A, Gurk-Turner C. Angiotensin II receptor blockers. Proc (Bayl Univ Med Cent). 2003;16(1):123-6.
20. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension. 2020;75(6):1334-57.
21. Scotti L, Bassi L, Soranna D, Verde A, Sultana J, de Paola G, et al. Association between renin-angiotensin-aldosterone system inhibitors and risk of dementia: a meta-analysis. Pharmacol Res. 2021;166:105515.
22. Chiu WC, Ho WC, Lin MH, Lee HH, Yeh YC, Wang JD, et al. Angiotension receptor blockers reduce the risk of dementia. J Hypertens. 2014;32(4):938-47.
23. Takeda S, Sato N, Takeuchi D, Kurinami H, Shinohara M, Niisato K, et al. Angiotensin receptor blocker prevented beta-amyloid-induced cognitive impairment associated with recovery of neurovascular coupling. Hypertension. 2009;54(6):1345-52.
24. Kehoe PG, Wilcock GK. Is inhibition of the renin-angiotensin system a new treatment option for Alzheimer's disease? Lancet Neurol. 2007;6(4):373-8.
25. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ. 2010;340:b5465.
26. Deng Z, Jiang J, Wang J, Pan D, Zhu Y, Li H, et al. Angiotensin receptor blockers are associated with a lower risk of progression from mild cognitive impairment to dementia. Hypertension. 2022;79(10):2159-69.
27. Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol. 2011;10(1):43-53.
28. Ho JK, Moriarty F, Manly JJ, Larson EB, Evans DA, Rajan KB, et al. Blood-brain barrier crossing renin-angiotensin drugs and cognition in the elderly: a meta-analysis. Hypertension. 2021;78(3):629-43.
29. Li ECK, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev. 2014;(8):CD009096.
30. Tully PJ, Helmer C, Peters R, Tzourio C. Exploiting drug-apolipoprotein E gene interactions in hypertension to preserve cognitive function: the 3-city cohort study. J Am Med Dir Assoc. 2019;20(2):188-194.e4.
31. Nation DA, Ho J, Yew B; Alzheimer's Disease Neuroimaging Initiative. Older adults taking AT1-receptor blockers exhibit reduced cerebral amyloid retention. J Alzheimers Dis. 2016;50(3):779-89.
32. World Health Organization. Basic tabulation list with alphabetical index. World Health Organization; 1978. https://iris.who.int/bitstream/handle/10665/39473/9241541334-eng.pdf?sequence=1&isAllowed=y
33. ICD-10 version:2019. https://icd.who.int/browse10/2019/en. Accessed 12 Aug 2023.

34. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC - ATC/DDD Index. https://www.whocc.no/atc_ddd_index. Accessed 12 Aug 2023.
35. Halpern R, Seare J, Tong J, Hartry A, Olaoye A, Aigbogun MS. Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia. Int J Geriatr Psychiatry. 2019;34(3):420-31.
36. Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, et al. Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching. J Alzheimers Dis. 2022;88(3):1061-74.
37. VanderWeele TJ. Principles of confounder selection. Eur J Epidemiol. 2019;34(3):211-9.
38. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167(4):268-74.
39. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374(21):2009-20.
40. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. Stat Med. 1995;14(15):1707-23.
41. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika. 1982;69(1):239-41.
42. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.
43. Asenjo RM, Bueno H, Mcintosh M. Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs). https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Treatment-goals/Cardio-Protective-drugs/angiotensin-converting-enzyme-inhibitors-ace-inhibitors-and-angiotensin-ii-rec (2017). Accessed 24 Aug 2023.
44. Barthold D, Joyce G, Wharton W, Kehoe P, Zissimopoulos J. The association of multiple antihypertensive medication classes with Alzheimer's disease incidence across sex, race, and ethnicity. PLoS One. 2018;13(11):e0206705.
45. Hemming ML, Selkoe DJ. Amyloid β-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. J Biol Chem. 2005;280(45):37644-50.
46. Zou K, Yamaguchi H, Akatsu H, Sakamoto T, Ko M, Mizoguchi K, et al. Angiotensin-converting enzyme converts amyloid beta-protein 1-42 (Abeta(1-42)) to Abeta(1-40), and its inhibition enhances brain Abeta deposition. J Neurosci. 2007;27(32):8628-35.
47. Sun X, Chen WD, Wang YD. β-Amyloid: the key peptide in the pathogenesis of Alzheimer's disease. Front Pharmacol. 2015;6:221.
48. O'Brien JT, Thomas A. Vascular dementia. Lancet. 2015;386(10004):1698-706.
49. Glodzik L, Santisteban MM. Blood-brain barrier crossing renin-angiotensin system drugs: considerations for dementia and cognitive decline. Hypertension. 2021;78(3):644-6.
50. Ho JK, Nation DA; Alzheimer's Disease Neuroimaging Initiative. Memory is preserved in older adults taking AT1 receptor blockers. Alzheimers Res Ther. 2017;9(1):33.
51. Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. Arch Neurol. 2011;68(2):214-20.
52. Kujovic M, Lipka T, Zalman M, Baumann L, Jänner M, Baumann B. Treatment of hypertension and obstructive sleep apnea counteracts cognitive decline in common neurocognitive disorders in diagnosis-related patterns. Sci Rep. 2023;13(1):7556.
53. Groenwold RHH, Palmer TM, Tilling K. To adjust or not to adjust? When a "confounder" is only measured after exposure. Epidemiology. 2021;32(2):194-201.
54. Haan MN, Mayeda ER. Apolipoprotein E genotype and cardiovascular diseases in the elderly. Curr Cardiovasc Risk Rep. 2010;4(5):361-8.