




Article

Angiotensin II Receptor Blockers Reduce Tau/A β 42 Ratio: A Cerebrospinal Fluid Biomarkers' Case-Control Study

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Abstract: (1) Background: The role of antihypertensives in Alzheimer's Disease (AD) prevention is controversial. This case-control study aims to assess whether antihypertensive medication has a protective role by studying its association with amyloid and tau abnormal levels. Furthermore, it suggests a holistic view of the involved pathways between renin-angiotensin drugs and the tau/amyloid β 42 ratio (tau/A β 42 ratio); (2) Methods: The medical records of the participant patients were reviewed, with a focus on prescribed antihypertensive drugs and clinical variables, such as arterial blood pressure. The Anatomical Therapeutic Chemical classification was used to classify each drug. The patients were divided into two groups: patients with AD diagnosis (cases) and cognitively healthy patients (control); (3) Results: Age and high systolic blood pressure are associated with a higher risk of developing AD. In addition, combinations of angiotensin II receptor blockers are associated with a 30% lower t-tau/A β 42 ratio than plain angiotensin-converting enzyme inhibitor consumption; (4) Conclusions: Angiotensin II receptor blockers may play a potential role in neuroprotection and AD prevention. Likewise, several mechanisms, such as the PI3K/Akt/GSK3 β or the ACE1/AngII/AT1R axis, may link cardiovascular pathologies and AD presence, making its modulation a pivotal point in AD prevention. The present work highlights the central pathways in which antihypertensives may affect the presence of pathological amyloid and tau hyperphosphorylation.

Keywords: Alzheimer's disease; antihypertensives; amyloid; tau; angiotensin-converting enzyme inhibitor; angiotensin II receptor blockers; therapeutic strategies; personalized medicine



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1. Introduction

Alzheimer's Disease (AD) is associated with alterations in the amyloid beta peptide (A β) and tau proteins, as well as changes in cholinergic function [1–3]. The main AD cerebrospinal fluid (CSF) biomarkers are amyloid - β 42- (A β 42), total tau (t-tau), hyperphosphorylated tau (p-tau), and the tau/A β 42 ratio [4]. First, CSF A β 42 levels decrease in the development of the disease [5], which represents a reduced clearance from the brain into the blood, resulting in a higher accumulation of A β plaques in the brain [6]. Second, the tau protein stabilizes microtubules in normal conditions as a compensatory mechanism against oxidative stress and A β toxicity, and GSK3 β regulates its phosphorylation [7]. Elevated CSF tau levels are associated with neurodegeneration and are statistically associated with the progression from mild cognitive impairment to AD, and p-tau elevation reflects the formation of neurofibrillary tangles in the brain [8].

Since AD has a long asymptomatic period, risk factors such as hypertension are involved in its progression [1,9,10]. Hypertension is associated with a doubling in the likelihood of developing AD [2,9,11,12], and this risk increases if hypertension persists over the years [13]. In addition, hypertension causes oxidative stress and endothelial

dysfunction, leading to blood vessel atrophy, which becomes particularly important with aging and is associated with cognitive impairment and increased A β deposition in the brain [12].

Antihypertensives are of interest in dementia prevention due to their cerebrovascular structure protection and other mechanisms besides blood pressure control [13–16]. Nevertheless, not all antihypertensives have the same influence on AD, as their mechanisms of action differ. Antiadrenergic agents, such as the α -1-adrenoceptor antagonists, decrease peripheral vascular resistance [17] and are associated with (A β) modulation [15,18]. On the other hand, diuretics may minimize cerebrovascular events and act on A β peptides [15]. Vasodilator drugs enhance nitric oxide (NO), the role of which in AD is controversial [19]. Otherwise, diosmin stands out among the vascular vasoprotective agents because it reduces A β and p-tau formation in mouse models [20], and β -blockers may have the same effect on AD hallmarks [15]. Finally, calcium channel blockers (CCB) are highlighted due to their neuroprotective properties [15,21–24] and, along with the renin-angiotensin system (RAS)-acting agents, they both appear to be the most effective option in AD risk modulation [16]. In this sense, the angiotensin-converting enzyme inhibitors (ACEi) and the angiotensin II receptor blockers (ARBs) stand out as the main drugs acting on the RAS system. They both are associated with AD risk reduction, but their mechanisms of action differ. While the ACEi prevent the inactivation of bradykinin and the formation of Angiotensin II (1–8), affecting AT1R and AT2R [25,26], ARBs are AT1 receptor antagonists, and, therefore, they enhance AT2, Ang IV, and Ang (1–7) receptors [3,25–29].

For all the above, the present study aims to evaluate the associations between antihypertensive treatments and AD CSF biomarkers.

2. Materials and Methods

2.1. Participants and Study Design

The present work is a retrospective case-control study conducted at the Neurology Unit of the University and Polytechnic Hospital La Fe (Valencia, Spain). The Ethics Committee for Biomedical Research at CEU Cardenal Herrera University and the Medicaments Research Ethics Committee at the Health Research Institute Hospital La Fe have approved this study (CEI21/052 and 202-705-1).

The participants were recruited through a medical interview between January 2017 and December 2020. The enrolled patients received information and signed the informed consent, following the Declaration of Helsinki, the Good Clinical Practices, and local regulations.

The inclusion criteria for this study were to be between 50 and 80 years old, sign the informed consent, and have medical records of CFS biomarkers (A β 42, t-tau, p-tau), neuropsychological evaluation, and medication intake. The exclusion criteria for the present study were not to meet the inclusion criteria, be enrolled in a clinical trial, have other neurological diseases such as epilepsy, multiple sclerosis, or brain damage, or have psychiatric disorders, such as depression (major disorder) or bipolar disorder. In addition, patients with severe dementia or previous disabilities were excluded.

The patients' diagnoses were based on The National Institute on Aging-Alzheimer's Association clinical criteria [30]. Therefore, a neuropsychological evaluation based on the Clinical Dementia Rating (CDR) [31], the Repeatable Battery for the Assessment of Neuropsychological Status-Delayed Memory (RBANS.DM) [32], the Mini-Mental State Examination (MMSE) [33], the Functionality Assessment Questionnaire (FAQ) [34], and the AD Cooperative Study ADL Scale for Mild Cognitive Impairment (SDCS-ADL-MCI) [35] were performed. In addition, neuroimaging and CFS biomarkers (β 42, t-tau, p-tau, tau/A β 42 ratio) were assessed. Patients were "and tau/A β 42 ratio were found. Neuropsychological evaluation was considered to optimize a patient's diagnosis and establish a patient's cognitive decline stage. Patients with normal CSF levels and who were cognitively healthy were classified as control participants. All efforts were made to include a biologically defined control group (CSF biomarkers) in the study.

2.2. Data Source and Variables

The patients were anonymized, and the electronic health system was used to perform an exhaustive review of their medical records at the Polytechnic University Hospital La Fe (Valencia). Thus, age, sex, smoking history, and comorbidities such as hypertension were registered. Furthermore, total and high-density lipoprotein (HDL) cholesterol, as well as blood pressure levels, were calculated from the average of two or more measurements, preferably within six months before or after diagnosis. Those variables were gathered at the participant's hospital and related healthcare centers.

CSF samples were obtained as part of the diagnosis protocol at the Polytechnic University Hospital La Fe (Valencia). From 5 to 10 mL of CSF was collected and stored at -80°C until analysis. Biochemical determinations ($\text{A}\beta_{42}$, t-tau, p-tau) were carried out by a chemiluminescence immunoassay [36]. Specifically, the CSF biomarker cut-off established for t-tau/ $\text{A}\beta_{42}$ was >0.51 and was >485 , >56 , and <725 pg/mL for t-tau, p-tau, and $\text{A}\beta_{42}$, respectively [37].

An antihypertensive treatment prescription was acquired by a medical history review, and it was registered by Yes/No using the Anatomical Therapeutic Chemical (ATC) code of the WHO Collaborating Centre for Drug Statistics Methodology (WHO) "https://www.whocc.no/atc_ddd_index/" (accessed on 1 May 2021)". ATCs were firstly regrouped and analyzed by therapeutic subgroup (2nd ATC level) and, secondly, by introducing agents acting on the RAS as their pharmacological subgroup (3rd level). As for the C02 ATC group, only doxazosin was found. Thus, for greater clarity, reference to this group will be made directly to this active ingredient. The same situation was performed with vasoprotective medication, with calcium dobesilate as the representative drug. Finally, the duration of treatment was represented in months.

2.3. Statistical Analysis

The data were summarized using the median (1st and 3rd quartiles) for the numeric variables and the absolute frequency (%) for the qualitative variables. The biomarkers were log-transformed to avoid skewed data.

On the one hand, logistic regression models were performed to assess the relationship between clinical classification attending to CSF biomarkers (AD group, control group) and age, gender, and systolic and diastolic blood pressure. In addition, 2-way interactions with systolic blood pressure (SBP), X "antihypertensives", diastolic blood pressure (DBP) X "antihypertensives", and hypertension X "antihypertensives" were explored. Finally, conditional effects with their 95% CI were depicted.

On the other hand, elastic net linear regression models were adjusted for each biomarker (β_{42} amyloid, t-tau, p-tau, and t-tau/ β_{42} ratio) to select their associated characteristics. The general model included the following variables: age, sex, SBP, DBP, diabetes mellitus type 2, total cholesterol, smoking habit, number of chronic treatments, and antihypertensive drugs intake (doxazosin, diuretics, peripheral vasodilators, calcium dobesilate, beta-blocking agents, calcium channel blockers, plain ACEi, combinations of ACEi, plain ARBs, and combinations of ARBs).

The elastic net regularization method of the estimated beta coefficients improves upon ordinary least squares. It linearly combines the L1 and L2 penalties of the lasso and ridge methods. The regularization parameter λ determines the amount of regularization. An optimal value for λ was determined by performing a 10-fold cross-validation, which yielded the minimum cross-validated mean-squared error (CVM). A median of 1000 repetitions of the cross-validation was calculated to improve lambda's robustness.

The ARBs and ACEi and their relation to t-tau/ β_{42} amyloid were analyzed by multi-variable logistic regression. Multiple comparisons were performed to assess the differences in the before-mentioned groups. The goodness of fit for the adjusted model was carried out using simulated scale residual diagnostics.

All the statistical analyses were performed using R (V. 4.0.3.) and the packages glmnet (V.4.1-3), click (V.0.8.0), ggeffects (V.1.1.1), ggplot2 (V.3.3.5), and DHARMa (V. 0.4.4).

3. Results

3.1. Participants

Seven hundred and forty-six participants were enrolled in the present study. From these, duplicated records due to follow-up ($n = 31$), patients without CSF biomarkers ($n = 143$), those diagnosed with other dementias (non-AD), or those with moderate or severe dementia due to AD ($n = 273$) were not included. Finally, the patients without medical records of total cholesterol levels or blood pressure ($n = 17$) or with the simultaneous prescription of ARBs or ACEi ($n = 2$) were excluded (see Figure 1).

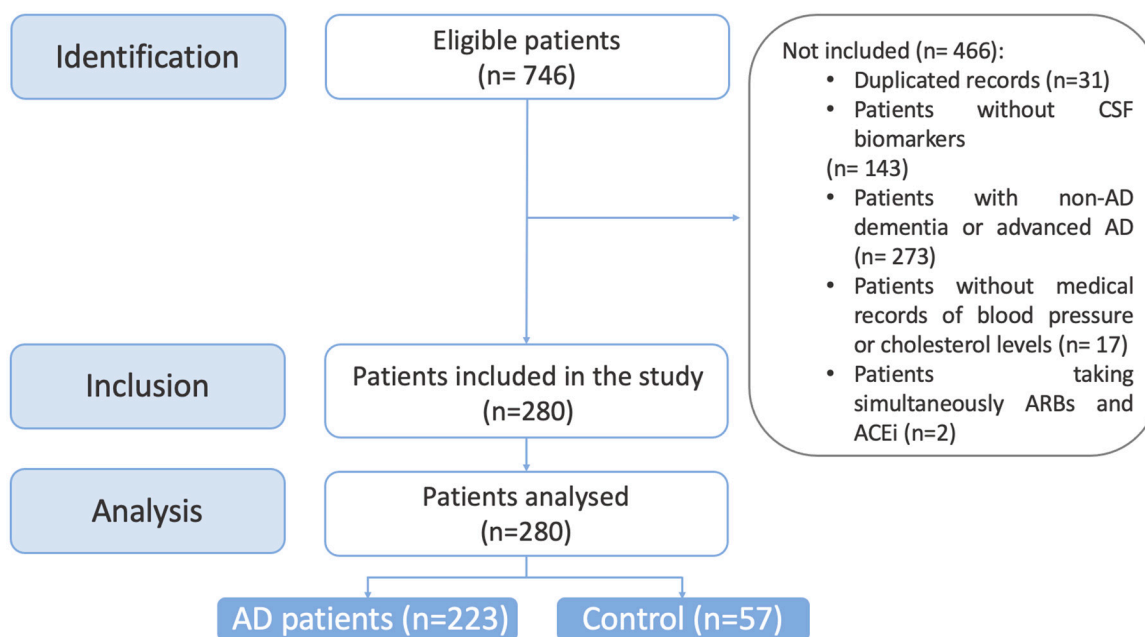


Figure 1. STROBE participant's selection flow chart. ACEi= angiotensin-converting enzyme inhibitor; AD = Alzheimer's Disease; ARBs = angiotensin II receptor blockers; CSF = cerebrospinal fluid.

From the initial cohort, 280 patients were included. They were classified as AD and cognitively healthy patients, according to their CSF levels. Thus, 57 participants were considered cognitively healthy patients (controls) and 223 were considered AD patients (cases), of whom 160 patients (71.75%) had mild cognitive impairment due to AD and 63 patients (28.25%) had mild dementia due to AD.

3.2. Demographic and Clinical Data of Participants

Table 1 shows the demographic and clinical variables for each group of participants. As can be seen, the AD patients were older than the controls, were predominantly female, and had more chronic concomitant medications prescribed.

Table 1. Demographic and clinical variables for the participants' groups.

Variable	AD (n = 223)	Control (n = 57)
Age (years, median (IQR))	71 (67.5, 74)	65 (62, 69)
Sex (female, n (%))	135 (60.54%)	25 (43.86%)
CSF biomarkers		
A β 42 levels (pg/mL, median (IQR))	600 (468.04, 702.1)	1206.15 (996, 1472)
t-tau levels (pg/mL, median (IQR))	586 (414, 837)	240 (182, 313)
p-tau levels (pg/mL, median (IQR))	92 (72.5, 131)	42 (32, 56)
Ratio t-tau/A β 42 (median (IQR))	0.94 (0.68, 1.43)	0.19 (0.14, 0.24)

Table 1. Cont.

Variable	AD (n = 223)	Control (n = 57)
Smoking history		
No (n, %)	145 (65.02%)	34 (59.65%)
No (Ex-smoker), (n, %)	45 (20.18%)	10 (17.54%)
Yes (n, %)	33 (14.8%)	13 (22.81%)
Number of concomitant medications		
	5 (3, 7)	3 (2, 5)
Total cholesterol (mg/dL, median (IQR))	189 (165.25, 212)	196 (170, 222)
HDL cholesterol (mg/dL, median (IQR))	55.5 (47, 66.25)	55 (44, 67.6)
Lipid-modifying agents (n, %)	123 (55.16%)	28 (49.12%)
Antidiabetic drugs (n, %)	36 (16.14%)	11 (19.3%)
Systolic blood pressure (mmHg, median (IQR))	135 (124.58, 143.42)	130 (118, 139)
Diastolic blood pressure (DBP) (mmHg, median (IQR))	75 (70, 81)	78 (71, 82.5)
Hypertension (n, %)	122 (54.71%)	30 (52.63%)

A β 42 = β amyloid 42; CSF = cerebrospinal fluid; dL = deciliter; IQR = interquartile range; mg = milligrams; mL = milliliters; mmHg = millimeters of mercury; n = number of patients; pg = picograms; p-tau = phosphorylated tau; t-tau = total tau.

Regarding cardiovascular risk factors, the patients with AD were predominantly non-smokers and had lower total cholesterol levels. In contrast, they had a greater rate of lipid-modifying prescription, SBP levels, and hypertension than the control patients. However, the control patients were more prone to taking antidiabetic drugs and having higher DBP than the case group (Table 1).

3.3. Hypertension and Alzheimer's Disease

Multivariate logistic regression was performed. In addition, age, gender, and blood pressure levels were analyzed and compared to the presence of AD. SBP and antihypertensive prescription statistical interaction were explored without significant differences. Thus, the [SBP \times antihypertensive intake] interaction was removed.

A positive association was found between the likelihood of suffering from AD and age (OR = 1.174, IC95% [1.105; 1.255], p -value < 0.001) and higher SBP (OR = 1.036, IC95% [1.004; 1.071], p -value = 0.033). On the contrary, men seemed less likely to develop AD than women despite the result being non-significant (OR = 0.513, IC95% [0.246; 1.051], p -value = 0.07). No differences were found regarding diastolic blood pressure and antihypertensive intake (see Table S1 of Supplementary Information).

3.4. Antihypertensive Drugs and Alzheimer's Disease Biomarkers

Each therapeutic subgroup prescription was examined to assess whether antihypertensive drugs are associated with AD (Table 2). As can be seen, the AD patients were older when the first antihypertensive drug was prescribed and took the medication for more years. In addition, β -blocking agents and CCB were consumed more among the AD patients, whereas diuretics and agents acting on RAS were the most common drugs among the control patients.

Moreover, all the models associated older age with impaired CFS biomarkers levels (Table 3). Additionally, a trend was observed between antidiabetic consumption and higher A β 42 and lower t-tau/A β 42, whereas being male seemed to be linked to lower t-tau levels. CCB seemed to be associated with a higher t-tau/ β 42 amyloid ratio. Finally, plain ACEi drugs were associated with higher t-tau and t-tau/ β 42 amyloid levels, whereas combinations of ARBs were related to lower levels of this biomarker.

Table 2. Antihypertensive prescription for the participants' groups.

Variable	AD (n = 223)	Control (n = 57)
Antihypertensive drugs prescription (n, %)	116 (52.02%)	29 (50.88%)
Age at first prescribed antihypertensive treatment (years, median (IQR))	61 (58, 65)	56 (53, 62)
Years since 1st antihypertensive treatment prescription (years, median (IQR))	7 (0, 11)	2 (0, 10)
Number of antihypertensives daily intake (n, %)		
0	107 (47.98%)	28 (49.12%)
1	59 (26.46%)	11 (19.3%)
2	40 (17.94%)	11 (19.3%)
3	16 (7.17%)	6 (10.53%)
4	1 (0.45%)	0 (0%)
5	0 (0%)	1 (1.75%)
Doxazosin prescription (n, %)	2 (0.9%)	2 (3.51%)
Diuretics prescription (n, %)	9 (4.04%)	3 (5.26%)
Peripheral vasodilators (n, %)	3 (1.35%)	1 (1.75%)
Calcium dobesilate prescription (n, %)	0 (0%)	1 (1.75%)
Beta-blocking agents prescription (n, %)	20 (8.97%)	1 (1.75%)
Calcium channel blockers prescription (n, %)	36 (16.14%)	8 (14.04%)
Agents acting on the renin-angiotensin system (n, %)	90 (40.36%)	25 (43.86%)

IQR = Interquartile range; n = number of patients.

Table 3. Elastic net model for CSF biomarkers (A β 42, p-tau, t-tau, ratio t-tau/A β 42) from antihypertensive variables.

Variable	A β 42 Model (Estimate)	p-tau Model (Estimate)	t-tau Model (Estimate)	Ratio tau/A β 42 Amyloid Model (Estimate)
Sex (male)	-	-	-0.087	-0.1
Age	-0.015	0.015	0.024	0.047
Antidiabetic drugs	0.043	-	-	-0.035
Total cholesterol (mg/dL)	-	-	-0.001	-0.001
Diastolic blood pressure	-	-	-0.002	-
Number of antihypertensives	0	-	-	-
Doxazosin prescription	0.123	-	-0.107	-0.481
Calcium dobesilate prescription	0.175	-	-	-0.421
Calcium channel blockers	-	-	-	0.053
ACEi, plain	-	-	0.059	0.05
ARBs, combinations	-	-	-0.041	-0.206
lambda	0.067	0.123	0.069	0.075

Alpha = 0.5. ACEi = Angiotensin-converting enzyme inhibitors; ARBs = Angiotensin receptor blockers; A β 42 = β amyloid 42; dL = deciliter; p-tau = phosphorylated tau; t-tau = total tau.

3.5. ACEi and ARBs Pharmacological Subgroups

Since ARBs and ACEi showed opposite t-tau/A β 42 ratio effects (Table 3), a deeper analysis was performed (Table 4). As a result, it was observed that a significant propor-

tion of the patients with AD were taking ACEi, whereas ARBs were the most consumed drugs among the control patients. Moreover, almost all the control patients were taking plain ACEi.

Table 4. Renin-angiotensin drugs subgroups consumption between AD and control patients.

Variable	AD	Control
Angiotensin-converting enzyme inhibitors prescription (n, (%))	40 (17.94)	5 (8.77)
Angiotensin-converting enzyme inhibitors prescription duration (months, median (IQR))	42 (11, 106)	19 (1, 48)
Plain angiotensin-converting enzyme inhibitors prescription (n, (%))	30 (13.45)	1 (1.75)
Combinations of angiotensin-converting enzyme inhibitors prescription (n, (%))	10 (4.48%)	4 (7.02%)
Angiotensin-converting enzyme inhibitors prescription without medical records of angiotensin II receptor blockers prescription (n, (%))	33 (14.8%)	4 (7.02%)
Angiotensin II receptor blockers prescription (n, (%))	50 (22.42%)	20 (35.09%)
Angiotensin II receptor blockers duration (months, median (IQR))	83 (56.75, 118.75)	69 (39, 95)
Plain angiotensin II receptor blockers (n, (%))	21 (9.42%)	7 (12.28%)
Combinations of angiotensin II receptor blockers (n, (%))	29 (13%)	12 (21.05%)
Angiotensin II receptor blockers prescription without medical records of angiotensin-converting enzyme inhibitors prescription (n, (%))	43 (19.28)	18 (31.58)

IQR = Interquartile range; n = number of patients.

Firstly, it was observed that the consumption of ARBs was significantly associated with a lower t-tau/A β 42 ratio when compared to ACEi (see Figure 2).

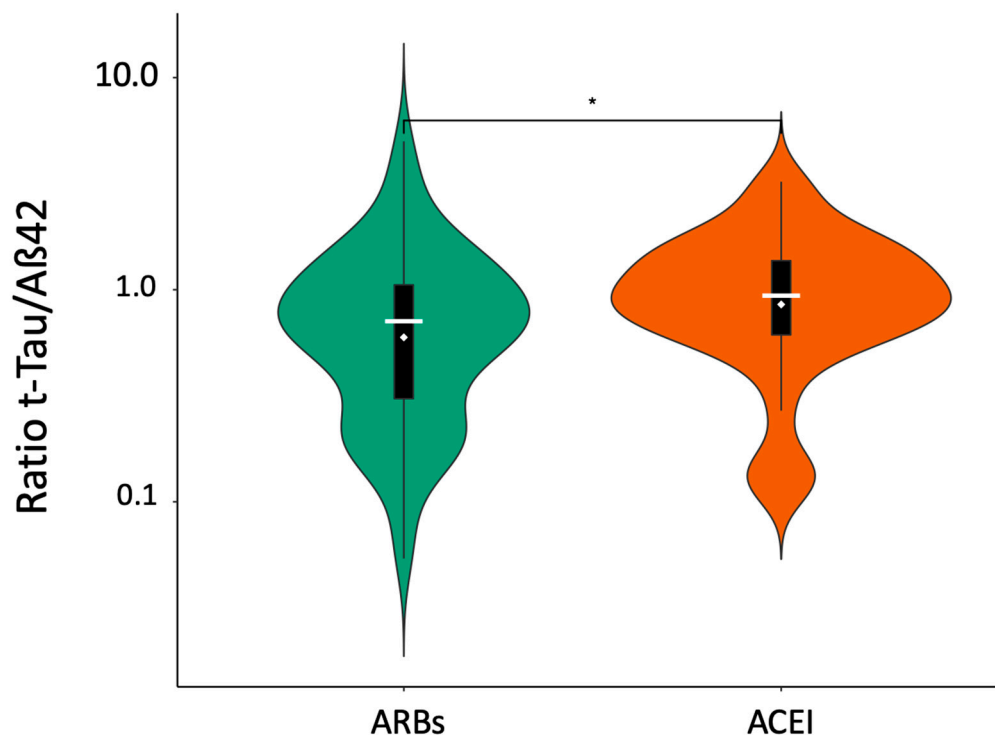


Figure 2. Comparison of ARBs and ACEi consumption with t-tau/A β 42 ratio values using violin model. * = Level of significance is provided by Wilcox Test. A β 42 = Amyloid beta 42; ACEi = Angiotensin-converting enzyme inhibitors; ARBs = Angiotensin receptor blockers; t-tau = total CSF tau levels; t-tau = total tau.

Secondly, multivariable logistic regression was performed to confirm the abovementioned results and predict the t-tau/A β 42 ratio association with ARBs and ACEi (see Table S2). The model included sex and age as covariables because they seemed to be the variables with the strongest association with AD. It was observed that combinations of ARBs consumption were associated with a 30% lower t-tau/A β 42 ratio than plain ACEi consumption (estimate = -0.334 , IC95%, [-0.613 , -0.055], p -value = 0.019).

Thirdly, statistical differences in the t-tau/A β 42 ratio between patients taking combinations of ARBs and patients consuming plain ACEi were observed (estimate = -0.5242 , IC95% (-0.1984 ; -2.643), p -value = 0.026), as well as between patients taking combinations of ARBs and those not taking plain ACEi or combinations of ARBs (estimate = -0.3339 , IC95% (0.1418 ; -2.354), p -value = 0.0485) (Figure 3).

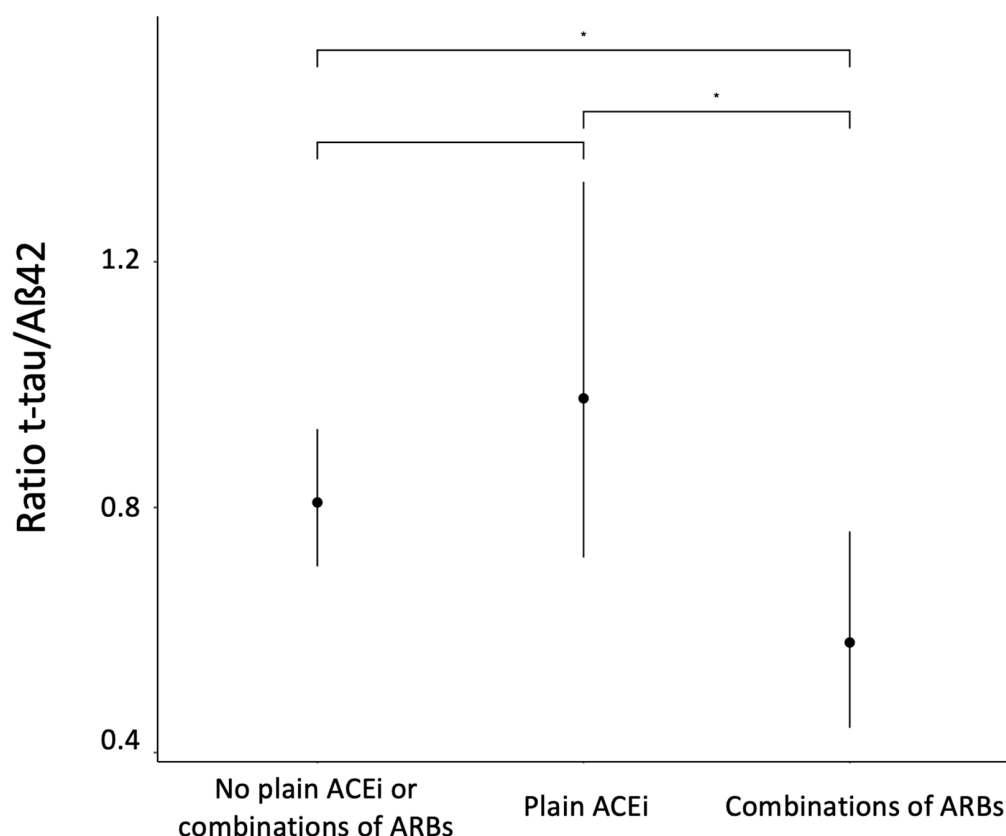


Figure 3. Conditional effects of t-tau/A β 42 ratio to combination ARBs and plain ACEi and Tukey multiples comparisons. Adjusted for age = 69 years, female. (*) = p -value < 0.05. β 42 = Amyloid beta 42; ACEi = Angiotensin-converting enzyme inhibitors; ARBs = Angiotensin receptor blockers; t-tau = total tau.

4. Discussion

The present study compares the differences between the different antihypertensive treatments and the alteration of fluid biomarkers for AD. Previous studies point out that antihypertensive medication is associated with AD risk reduction, but they are mainly based on cognitive test evolution or dementia diagnosis conversion [22,38,39]. In order to follow a standardized biological criterion, CSF biomarkers were used in AD diagnosis. To our knowledge, this is one of the few antihypertensive studies in AD that defines case and control groups based on CSF biomarker levels. For instance, a clinical trial performed in 2012 about ACEi modulation of ACEs activity in CSF included fourteen volunteers [40]. Moreover, the study of Hestad and co-workers included eight patients with subjective memory complaints as a control group out of 72 subjects [8]. Finally, Nation et al. performed a study of antihypertensives based on CSF AD biomarkers in 2016, but it just included 124 patients [41].

This study shows that high SBP and AD are associated, which is consistent with the recent findings of Hestad et al. who found an association between SBP and CSF t-tau concentrations with lower delayed memory [8,41]. In addition, Affleck and co-workers showed in 2020 that the amyloid brain burden was lower in normotensive AD patients than in hypertensive AD patients [2]. Hypertension seems to be associated with an increase in β -secretase, the enzyme responsible for activating the amyloidogenic pathway of A β production, and an increase in the A β 42/A β 40 ratio [12]. In addition, several studies affirm that the association between SBP and dementia is significant in midlife but not later life [13]. Altogether, it seems that vascular damage is associated with AD. Due to the long period that elapses from when the pathological pathways begin to be altered until the first symptoms appear, it is possible in middle age when this factor becomes especially important.

Furthermore, this study compares the association between antihypertensive use and abnormal AD CSF biomarkers. A previous study performed by Affleck and co-workers in 2020 revealed that patients who take this medication have lower neurofibrillary tangle formation [2]. Nevertheless, when Hestad et al. compared antihypertensive consumption and cognitive functions, they showed worse cognitive function in the antihypertensive consumption group [8].

We did not observe AD diagnosis or CSF biomarker differences in our group compared to antihypertensive consumption per se. Nevertheless, it was observed that the AD patients received their first antihypertensive drug at an older age and for more years in our cohort than the control patients. Therefore, antihypertensives may not avoid AD development, but they may affect mild cognitive impairment or progression by minimizing vascular damage at the early stages and through mechanisms other than blood pressure control [16]. As a result, each antihypertensive class was analyzed separately and compared in four AD-biomarker models.

First, doxazosin prescription was associated with higher CSF A β 42 concentrations and lower t-tau and a lower tau/A β 42 ratio. In addition, despite scarce literature about doxazosin and AD biomarkers, a recent study showed that doxazosin prevented Akt reduction, avoiding tau phosphorylation in an in vitro model of organotypic hippocampal cultures exposed to A β [18]. However, our results must be taken carefully due to the reduced number of patients taking this drug in our cohort.

Regarding vasoprotective medication, calcium dobesilate releases NO, producing vasodilation [42,43]. The role of NO with biomarkers is controversial since it is involved in GSK-3 β activation and the consequent tau phosphorylation [19], as well as with Akt and cyclic-AMP-response-element-binding protein (CREB), which promotes cell survival and neuroprotection [44]. Recent studies indicate that an NO neuroprotective or neurotoxic effect depends on its concentration. It modulates heme-metals-A β binding and plays a key role in A β toxic effects [45]. In our cohort, calcium dobesilate seemed to be associated with higher CSF amyloid concentrations and a lower tau/A β 42 ratio. Nevertheless, only one patient was taking this antihypertensive in our sample, so further studies are needed to obtain conclusions.

As for beta-blocking agents, we did not observe any statistical difference between their consumption and AD hallmark alteration, which is consistent with previously published research [16].

In other matters, CCB highlights promising results in dementia prevention [15,22–24]. Intracellular calcium is elevated in elderly patients and plays a part in neurodegeneration, amyloid production enhancement, and tau hyperphosphorylation [15,16,23,46]. Thus, CCB may downregulate intracellular calcium levels and slow amyloid production [16,23]. In addition, CCB can enhance cerebral vascularization [15] and, in the case of nimodipine, can act as a cerebral vasodilator [46]. Among CCB, the dihydropyridine compounds stand out with promising results in A β 42 clearance [21,23]. Nevertheless, as shown in the work of Bachmeier et al., not all the dihydropyridines have the same effect on brain vasculature, and their effect on A β 42 clearance may not depend on blood–brain barrier (BBB) penetration. Whereas drugs such as nimodipine or nitrendipine are likely to enhance A β clearance from

the blood to the brain; others, such as amlodipine or nifedipine, do not seem to facilitate A β 42 transcytosis across the BBB in *in vivo* models, despite the fact that all of them can cross the BBB [21].

When we analyzed our cohort, we noticed that CCB was associated with a higher tau/A β 42 ratio and that the most CCB consumed was amlodipine. Moreover, just one patient took nimodipine when the lumbar puncture was performed. A recent study by Sadleir Id and colleagues aimed to explore whether nimodipine could modify amyloid pathogenesis when it begins in mouse models, but it did not show any changes in the A β 42 or total A β levels nor amyloid plaque deposition [46]. In addition, it was shown in work performed by Murray and colleagues in 2002 that CCBs were not associated with dementia prevention. Most of the prescribed dihydropyridines in our study were the same that did not boost A β 42 clearance in a study performed by Bachmeier and colleagues in 2011 [21,39]. Moreover, in the Baltimore Longitudinal Study of Aging, CCB did not reduce the incidence risk of AD [47], an effect that was neither observed in the Ginkgo Evaluation of Memory Study [48] nor the NIVALD study, the phase III clinical trial that tested nivaldipine vs. placebo in AD patients [49].

Altogether, it could explain why we did not observe a protective effect in our sample, although further studies are needed to elucidate the exact mechanism by which amlodipine may increase the tau/A β 42 ratio.

Lastly, RAS drugs stand out among the antihypertensive drugs thanks to their potential ability to limit A β plaques [14] and neurofibrillary tangle formation [2,14]. There is evidence of a dysregulation of endogenous RAS activity in AD patients, which has been confirmed in post-mortem brain tissue [14,27]. As recently reviewed by Gouveia and colleagues, ARBs and ACEi may be more effective at preventing AD than other antihypertensives [14,16,24,29]. Nevertheless, the bibliography suggests that certain ACEi are associated with the risk of dementia [12], whereas ARBs may act as neuroprotectors [16,29]. As a result, studying the effects of both drugs and their influence on CSF AD biomarkers is of interest.

The ACEi mechanism of action prevents the formation of Angiotensin II (1–8) and the degradation of plasma bradykinin through ACE inhibition, thus, contributing to inflammation, vascular and blood–brain barrier permeability, and impaired cerebral flow [50–54].

Moreover, ACE1 degrades A β -42 into A β 40, its soluble form [3,55], and studies show that ACEi can modify ACEs activity in CSF [40]. As a result, if ACE becomes blocked by ACEi, the clearance of A β 42 may not succeed, and plaques may accumulate in the brain [41].

Conversely, ACE inhibition may enhance the bradykinin concentrations in plasma and B1R and B2R activity in microglial cells [56]. B2R expresses constitutively under normal conditions, is activated in acute inflammation [51,53,57–59], and has a higher affinity for bradykinin and Lys-bradykinin peptides [53,58]. However, B1R is upregulated by chronic inflammation [53,58,60] and has a higher affinity for Lys-des-Arg9-BK and des-Arg9-BK [50,51,53,57,58,61]. Moreover, the B1R-derived pro-inflammatory cytokine release may contribute to BBB permeability and its disruption [58], being an essential pathophysiological mediator of cerebrovascular dysfunction, neuroinflammation, and A β pathology in AD [62].

Furthermore, higher bradykinin levels are linked to A β deposition, and its presence may enhance B1R, accentuating amyloid toxicity. In addition, the A β 42-amyloid peptide can induce the plasma contact system and activate the kallikrein-kinin system (KKS) because of its negative charge [51,52,56]. As a result, an increase in bradykinin production takes place, enhancing cerebral inflammation and vascular permeability [50–54] and up-regulating bradykinin receptors again (Figure 4).

On the contrary, there is evidence that ARBs reduce the A β burden in mice models and can reduce p-tau and neurofibrillary tangles in the hippocampus [29]. Their neuroprotector effect is attributed, in part, to AT1R blockade while stimulating AT2R, AT4R, and MasR [63].

AT1R can release aldosterone and cause vasoconstriction, fluid retention, and the M1 phenotype of microglial cell activation, which releases pro-inflammatory cytokines [29,63].

In addition, AT1R is related to hypertension, heart dysfunction, brain ischemia, abnormal stress responses, BBB breakdown, and inflammation [64]. Thus, the AT1R/Ang II axis links to pro-inflammatory and prooxidant effects, increasing BBB permeability [3,29], as well as cognitive impairment and tau hyperphosphorylation through the activation of GSK3 β [14], which has an essential role in the modulation of insulin [7]. Moreover, microglial activation is higher in elderly patients, and A β pathogenesis may exacerbate this process [3].

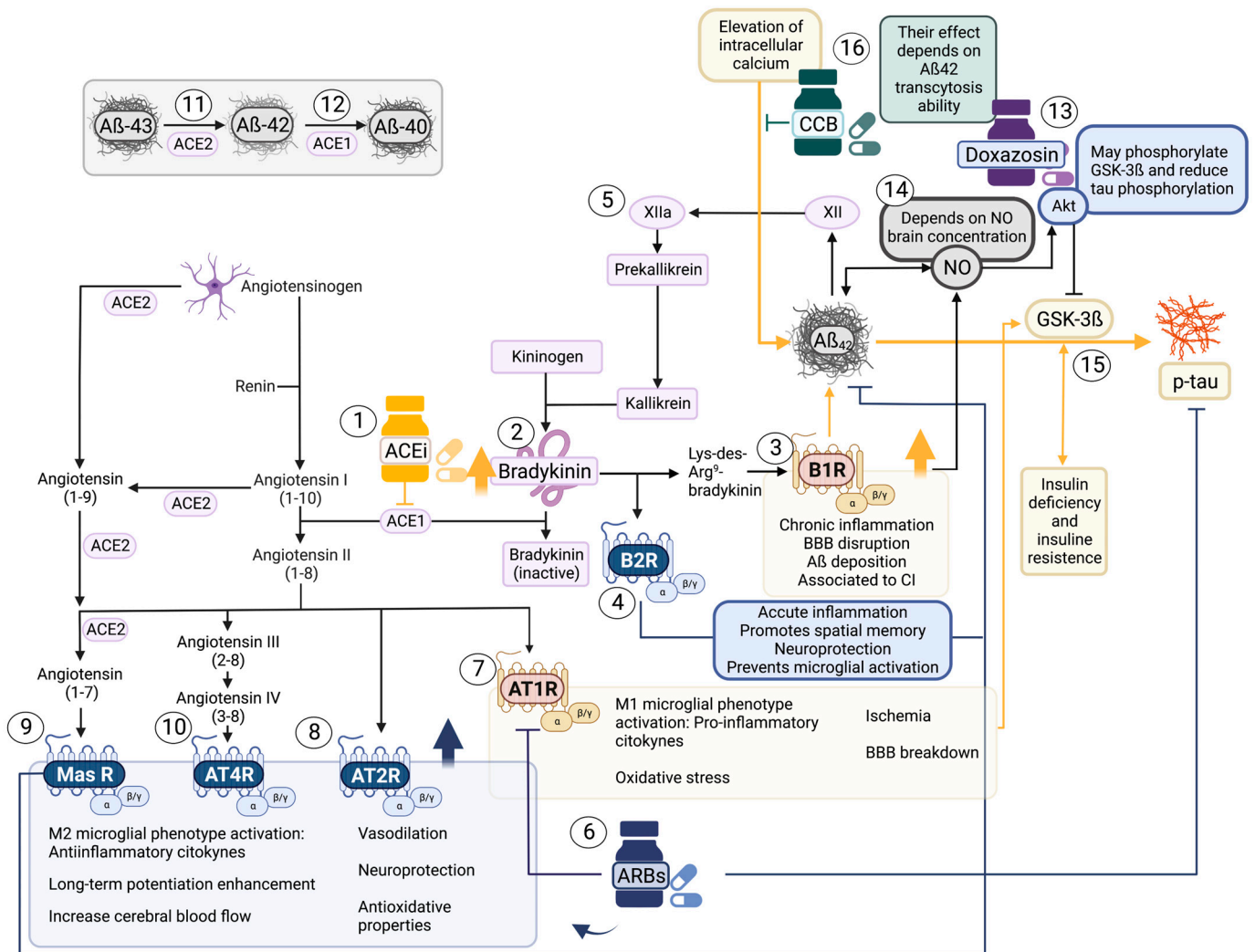


Figure 4. Proposed mechanism of action among antihypertensive drugs and CSF amyloid and tau alterations. Pathological processes are represented in yellow, whereas neuroprotective mechanisms appear in blue. Created with BioRender.com. A β 40 = Amyloid beta 40; A β 42 = Amyloid beta 42; ACEi = Angiotensin-converting enzyme inhibitors; ACE1 = Angiotensin-converting enzyme 1; ACE2 = Angiotensin-converting enzyme 2; Akt = Protein kinase B; ARBs = Angiotensin receptor blockers; AT1 = Angiotensin 1 Receptor; AT2 = Angiotensin 2 Receptor; AT4R = Angiotensin 4 Receptor; B1R = Bradykinin 1 receptor; B2R = Bradykinin 2 receptor; CCB = Calcium Channel Blocker; GSK-3 β = Glycogen synthase kinase 3 β ; MasR = Mitochondrial Assembly Receptor; NO = nitric oxide; p-tau = phosphorylated tau.

Conversely, AT2R causes angiogenesis, an NO increase, vasodilation, and the activation of the M2 phenotype of microglial cells, thereby releasing anti-inflammatory cytokines [29,63].

MasR produces anti-inflammatory, anti-oxidative, anti-fibrotic, vasodilation, and M2 activation effects [27,63], improving memory, learning, and long-period potentiation in

mouse models [27]. Finally, insulin-regulated aminopeptidase is associated with vasodilation and long-term potentiation enhancement [3,28].

Interestingly, AT1R is expressed more in the brain than AT2R [29]. As a result, drugs acting as AT1R antagonists may promote AT2R, MasR, and insulin-regulated activation, which may become significant in cognitive abilities. Other described mechanisms of action by which ARBs may have a protector role in AD are neuronal differentiation, DNA repair, the modulation of the cerebral microvasculature, the reversion of oxidative stress and inflammation, and ischemic brain injury prevention [41].

This work shows a positive association between the tau/A β 42 ratio and the use of ACEi, with an opposite effect when compared to using ARBs in combination (Figure 4). These findings are broadly consistent with slower A β [28,65] and tau progression when ARBs are consumed instead of ACEi.

The previously described mechanisms may explain why we observed a higher t-tau/A β 42 ratio in patients taking ACEi and its contrary effect in patients taking ARBs. Compared to published work, meta-analysis shows similar results in dementia risk prevention with ARBs consumption, whereas ACEi does not seem to reduce the risk of dementia [16,25] or reduce its risk less than ARBs [26]. In addition, the longitudinal study by Nation et al. in 2016 showed higher CSF A β 42 levels and lower p-tau levels over time when ARBs treated patients were compared to patients not taking antihypertensives. This study showed that A β 42 reduction was independent of age, the most influential risk factor of AD [41]. Finally, a meta-analysis performed by D'Silva et al. in 2022 shows how other clinical trials in which ARBs were compared to a placebo obtained conflicting results. One trial showed less deterioration in episodic memory and attention, whereas others did not show differences. Moreover, when compared to CBB, cognitive improvements were not observed, but an increase in cerebral blood flow in several brain regions, including the parietal lobe, was observed [26].

Finally, it must be noted that in our study, ARBs showed a protective effect in combination with diuretics, which is the most prescribed combination. In this sense, several studies pointed out the possible role of diuretics in AD risk reduction [38,48]. Their possible role may be due to the effect of these drugs on reducing cerebrovascular events, such as silent vascular lesions, that are involved in white matter changes, a common hallmark in AD and other dementias [38]. In addition, diuretics may act as AD risk reducers by their vasorelaxant effect, which may counteract the vasoconstriction produced by amyloid pathogenesis [38,48]. Among them, thiazide diuretics and potassium-sparing diuretics stand out as AD risk reducers in the Cache County study [22]. Thus, the protective role of ARBs could be enhanced by the neuroprotector properties that diuretics seem to have.

Strengths and Limitations

A strength of the present study is that the medications were registered according to exact dates and exact doses. In addition, the participants were classified as attending to CSF biomarkers levels, while most antihypertensive studies that correlate this medication with AD are based only on cognitive tests. In this sense, the present study provides an objective and accurate AD diagnosis.

It should be considered that the inclusion criteria for this study were to consent to a lumbar puncture, which is an invasive intervention that dissuades potential participants, especially cognitively healthy adults. In spite of the required invasive sampling with some adverse side effects (headaches, pain), a relevant number of cognitively healthy participants was included in the present study. This is a strength because, to our knowledge, there are few studies about antihypertensives with a control sample based on CSF biomarkers, and published work has a few participants. On the contrary, this fact is also a limitation, and future studies including more participants are needed.

Lastly, it must be considered that the study was performed at an outpatient consultation center of the Cognitive Disorders Unit, where other healthcare professionals refer

patients due to pathological suspicion or memory complaints. Moreover, adherence has not been verified, and genetic risk factors such as APOE e4 have not been analyzed.

5. Conclusions

High SBP, elderly age, and female gender are variables associated with a higher risk of AD diagnosis. In addition, calcium channel blockers and plain ACEi consumption are associated with a higher tau/A β 42 ratio, whereas consuming ARBs is associated with a lower tau/A β 42 ratio. Thus, ARBs should be considered a primary antihypertensive option for patients at risk of AD.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/pharmaceutics15030924/s1>, Table S1: Multivariate logistic regression to obtain the risk of AD from SBP and DBP and controlled by age, sex and antihypertensive intake; Table S2: Association between t-tau/A β 42 ratio and sex, age, ARBs and ACEi drugs; Table S3: Relationship between renin-angiotensin-system-acting agents and Alzheimer's Disease biomarkers.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Biomedical Research at CEU Cardenal Herrera University and the Medicaments Research Ethics Committee at the Health Research Institute Hospital La Fe (CEI21/052, 26MAY2021 and 202-705-1, 27JAN2021).

Informed Consent Statement: Informed consent was obtained from all the subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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References

1. Breijyeh, Z.; Karaman, R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules* **2020**, *25*, 5789. [[CrossRef](#)] [[PubMed](#)]
2. Affleck, A.J.; Sachdev, P.S.; Stevens, J.; Halliday, G.M. Antihypertensive medications ameliorate Alzheimer's disease pathology by slowing its propagation. *Alzheimer's Dement.* **2020**, *6*, e12060. [[CrossRef](#)]
3. Ribeiro, V.T.; de Souza, L.C.; Simões e Silva, A.C. Renin-Angiotensin System and Alzheimer's Disease Pathophysiology: From the Potential Interactions to Therapeutic Perspectives. *Protein Pept. Lett.* **2020**, *27*, 484–511. [[CrossRef](#)] [[PubMed](#)]
4. Álvarez, I.; Diez-Fairen, M.; Aguilar, M.; González, J.M.; Ysamat, M.; Tartari, J.P.; Carcel, M.; Alonso, A.; Brix, B.; Arendt, P.; et al. Added value of cerebrospinal fluid multimarker analysis in diagnosis and progression of dementia. *Eur. J. Neurol.* **2021**, *28*, 1142–1152. [[CrossRef](#)]
5. Peña-Bautista, C.; Roca, M.; López-Cuevas, R.; Baquero, M.; Vento, M.; Chafer-Pericas, C. Metabolomics study to identify plasma biomarkers in alzheimer disease: ApoE genotype effect. *J. Pharm. Biomed. Anal.* **2020**, *180*, 113088. [[CrossRef](#)] [[PubMed](#)]
6. Uddin, M.S.; Kabir, M.T.; Rahman, M.S.; Behl, T.; Jeandet, P.; Ashraf, G.M.; Najda, A.; Bin-Jumah, M.N.; El-Seedi, H.R.; Abdel-Daim, M.M. Revisiting the Amyloid Cascade Hypothesis: From Anti-A β Therapeutics to Auspicious New Ways for Alzheimer's Disease. *Int. J. Mol. Sci.* **2020**, *21*, 5858. [[CrossRef](#)]
7. Zhang, Y.; Huang, N.Q.; Yan, F.; Jin, H.; Zhou, S.Y.; Shi, J.S.; Jin, F. Diabetes mellitus and Alzheimer's disease: GSK-3 β as a potential link. *Behav. Brain Res.* **2018**, *339*, 57–65. [[CrossRef](#)]

8. Hestad, K.A.; Horndalsveen, P.O.; Engedal, K. Blood Pressure and T-Tau in Spinal Fluid Are Associated With Delayed Recall in Participants With Memory Complaints and Dementia of the Alzheimer's Type. *Front. Aging Neurosci.* **2021**, *13*, 685. [CrossRef]
9. Hahad, O.; Lelieveld, J.; Birklein, F.; Lieb, K.; Daiber, A.; Münzel, T. Ambient air pollution increases the risk of cerebrovascular and neuropsychiatric disorders through induction of inflammation and oxidative stress. *Int. J. Mol. Sci.* **2020**, *21*, 4306. [CrossRef]
10. Ramos, H.; Moreno, L.; Gil, M.; García-Lluch, G.; Sendra-Lillo, J.; Alacreu, M. Pharmacists' Knowledge of Factors Associated with Dementia: The A-to-Z Dementia Knowledge List. *Int. J. Environ. Res. Public Health* **2021**, *18*, 9934. [CrossRef]
11. Organización Mundial de la Salud. Envejecimiento y salud. *Cent Prensa OMS*. 2018, pp. 1–2. Available online: <https://www.who.int/es/news-room/fact-sheets/detail/envejecimiento-y-salud> (accessed on 5 May 2020).
12. Wahidi, N.; Lerner, A.J. Blood Pressure Control and Protection of the Aging Brain. *Neurotherapeutics* **2019**, *16*, 569–579. [CrossRef]
13. Livingston, G.; Huntley, J.; Sommerlad, A.; Ames, D.; Ballard, C.; Banerjee, S.; Brayne, C.; Burns, A.; Cohen-Mansfield, J.; Cooper, C.; et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* **2020**, *396*, 413–446. [CrossRef]
14. Wharton, W.; Zhao, L.; Steenland, K.; Goldstein, F.C.; Schneider, J.A.; Barnes, L.L.; Gearing, M.; Yasar, S. Neurofibrillary Tangles and Conversion to Mild Cognitive Impairment with Certain Antihypertensives. *J. Alzheimers Dis.* **2019**, *70*, 153–161. [CrossRef] [PubMed]
15. Leboviev, T.; Chen, Y.; Duriez, P.; Pasquier, F.; Bordet, R. Antihypertensive agents in Alzheimer's disease: Beyond vascular protection. *Expert Rev. Neurother.* **2020**, *20*, 175–187. [CrossRef]
16. den Brok, M.G.; van Dalen, J.W.; Abdulrahman, H.; Larson, E.B.; van Middelaar, T.; van Gool, W.A.; van Charante, E.P.; Richard, E. Antihypertensive Medication Classes and the Risk of Dementia: A Systematic Review and Network Meta-Analysis. *J. Am. Med. Dir. Assoc.* **2021**, *22*, 1386–1395. [CrossRef] [PubMed]
17. Carretero, M. Doxazosina | Offarm. *Doxazosina*. 2002, pp. 176–178. Available online: <https://www.elsevier.es/es-revista-offarm-4-articulo-doxazosina-13035880> (accessed on 24 April 2022).
18. Coelho, B.P.; Gaelzer, M.M.; dos Santos Petry, F.; Hoppe, J.B.; Trindade, V.M.; Salbego, C.G.; Guma, F.T. Dual Effect of Doxazosin: Anticancer Activity on SH-SY5Y Neuroblastoma Cells and Neuroprotection on an In Vitro Model of Alzheimer's Disease. *Neuroscience* **2019**, *404*, 314–325. [CrossRef]
19. Zhang, Y.-J.; Xu, Y.-F.; Liu, Y.-H.; Yin, J.; Wang, J.-Z. Nitric oxide induces tau hyperphosphorylation via glycogen synthase kinase-3 β activation. *FEBS Lett.* **2005**, *579*, 6230–6236. [CrossRef]
20. Sawmiller, D.; Habib, A.; Li, S.; Darlington, D.; Hou, H.; Tian, J.; Shytle, R.D.; Smith, A.; Giunta, B.; Mori, T.; et al. Diosmin reduces cerebral A β levels, tau hyperphosphorylation, neuroinflammation, and cognitive impairment in the 3xTg-AD Mice. *J. Neuroimmunol.* **2016**, *299*, 98. [CrossRef]
21. Bachmeier, C.; Beaulieu-Abdelahad, D.; Mullan, M.; Paris, D. Selective dihydropyridine compounds facilitate the clearance of β -amyloid across the blood-brain barrier. *Eur. J. Pharmacol.* **2011**, *659*, 124–129. [CrossRef]
22. Chuang, Y.F.; Breitner, J.C.; Chiu, Y.L.; Khachaturian, A.; Hayden, K.; Corcoran, C.; Tschanz, J.; Norton, M.; Munger, R.; Welsh-Bohmer, K.; et al. Use of diuretics is associated with reduced risk of Alzheimer's disease: The Cache County Study. *Neurobiol. Aging* **2014**, *35*, 2429–2435. [CrossRef] [PubMed]
23. Hwang, D.; Kim, S.; Choi, H.; Oh, I.H.; Kim, B.S.; Choi, H.R.; Kim, S.Y.; Won, C.W. Calcium-Channel Blockers and Dementia Risk in Older Adults—National Health Insurance Service—Senior Cohort (2002–2013). *Circ. J.* **2016**, *80*, 2336–2342. [CrossRef]
24. Barus, R.; Béné, J.; Deguil, J.; Gautier, S.; Bordet, R. Drug interactions with dementia-related pathophysiological pathways worsen or prevent dementia. *Br. J. Pharmacol.* **2019**, *176*, 3413–3434. [CrossRef]
25. Scotti, L.; Bassi, L.; Soranna, D.; Verde, F.; Silani, V.; Torsello, A.; Parati, G.; Zambon, A. Association between renin-angiotensin-aldosterone system inhibitors and risk of dementia: A meta-analysis. *Pharmacol. Res.* **2021**, *166*, 105515. [CrossRef] [PubMed]
26. D'Silva, E.; Meor Azlan, N.F.; Zhang, J. Angiotensin II Receptor Blockers in the Management of Hypertension in Preventing Cognitive Impairment and Dementia—A Systematic Review. *Pharmaceutics* **2022**, *14*, 2123. [CrossRef]
27. Evans, C.E.; Miners, J.S.; Piva, G.; Willis, C.L.; Heard, D.M.; Kidd, E.J.; Good, M.A.; Kehoe, P.G. ACE2 activation protects against cognitive decline and reduces amyloid pathology in the Tg2576 mouse model of Alzheimer's disease. *Acta Neuropathol.* **2020**, *139*, 485. [CrossRef] [PubMed]
28. Ouk, M.; Wu, C.Y.; Rabin, J.S.; Edwards, J.D.; Ramirez, J.; Masellis, M.; Swartz, R.H.; Herrmann, N.; Lanctôt, K.L.; Black, S.E.; et al. Associations between brain amyloid accumulation and the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. *Neurobiol. Aging* **2021**, *100*, 22–31. [CrossRef] [PubMed]
29. Gouveia, F.; Camins, A.; Ettcheto, M.; Bicker, J.; Falcão, A.; Cruz, M.T.; Fortuna, A. Targeting brain Renin-Angiotensin System for the prevention and treatment of Alzheimer's disease: Past, present and future. *Ageing Res. Rev.* **2022**, *77*, 101612. [CrossRef]
30. Albert, M.S.; DeKosky, S.T.; Dickson, D.; Dubois, B.; Feldman, H.H.; Fox, N.C.; Gamst, A.; Holtzman, D.M.; Jagust, W.J.; Petersen, R.C.; et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* **2011**, *7*, 270–279. [CrossRef]
31. Hughes, C.P.; Berg, L.; Danziger, W.L.; Coben, L.A.; Martin, R.L. A new clinical scale for the staging of dementia. *Br. J. Psychiatry* **1982**, *140*, 566–572. [CrossRef]
32. Randolph, C.; Tierney, M.C.; Mohr, E.; Chase, T.N. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *J. Clin. Exp. Neuropsychol.* **1998**, *20*, 310–319. [CrossRef]

33. Folstein, M.F.; Folstein, S.E.; McHugh, P.R. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* **1975**, *12*, 189–198. [[CrossRef](#)]
34. Pfeffer, R.I.; Kurosaki, T.T.; Harrah, C.H.; Chance, J.M.; Filos, S. Measurement of functional activities in older adults in the community. *J. Gerontol.* **1982**, *37*, 323–329. [[CrossRef](#)] [[PubMed](#)]
35. Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzheimer Dis. Assoc. Disord.* **1997**, *11*, 33–39. [[CrossRef](#)]
36. Peña-Bautista, C.; López-Cuevas, R.; Cuevas, A.; Baquero, M.; Cháfer-Pericás, C. Lipid peroxidation biomarkers correlation with medial temporal atrophy in early Alzheimer Disease. *Neurochem. Int.* **2019**, *129*, 104519. [[CrossRef](#)]
37. Peña-Bautista, C.; Álvarez-Sánchez, L.; Ferrer, I.; López-Noguerol, M.; Cañada-Martínez, A.J.; Oger, C.; Galano, J.M.; Durand, T.; Baquero, M.; Cháfer-Pericás, C. Lipid Peroxidation Assessment in Preclinical Alzheimer Disease Diagnosis. *Antioxidants* **2021**, *10*, 1043. [[CrossRef](#)]
38. Guo, Z.; Fratiglioni, L.; Zhu, L.; Fastbom, J.; Winblad, B.; Viitanen, M. Occurrence and Progression of Dementia in a Community Population Aged 75 Years and Older Relationship of Antihypertensive Medication Use. *Arch. Neurol.* **1999**, *56*, 991–996. [[CrossRef](#)] [[PubMed](#)]
39. Murray, M.D.; Lane, K.A.; Gao, S.; Evans, R.M.; Unverzagt, F.W.; Hall, K.S.; Hendrie, H. Preservation of cognitive function with antihypertensive medications: A longitudinal analysis of a community-based sample of African Americans. *Arch. Intern. Med.* **2002**, *162*, 2090–2096. [[CrossRef](#)]
40. Wharton, W.; Stein, J.H.; Korcarz, C.; Sachs, J.; Olson, S.R.; Zetterberg, H.; Dowling, M.; Ye, S.; Gleason, C.E.; Underbakke, G.; et al. The Effects of Ramipril in Individuals at Risk for Alzheimer's Disease: Results of a Pilot Clinical Trial NIH Public Access. *J. Alzheimers. Dis.* **2012**, *32*, 147–156. [[CrossRef](#)] [[PubMed](#)]
41. Nation, D.A.; Ho, J.; Yew, B. Older Adults Taking AT1-Receptor Blockers Exhibit Reduced Cerebral Amyloid Retention. *J. Alzheimer's Dis.* **2016**, *50*, 779–789. [[CrossRef](#)]
42. Angulo, J.; Cuevas, P.; Fernández, A.; Gabancho, S.; Videla, S.; Sáenz De Tejada, I. Calcium dobesilate potentiates endothelium-derived hyperpolarizing factor-mediated relaxation of human penile resistance arteries. *Br. J. Pharmacol.* **2003**, *139*, 854. [[CrossRef](#)]
43. Ruiz, E.; Lorente, R.; Tejerina, T. Effects of calcium dobesilate on the synthesis of endothelium-dependent relaxing factors in rabbit isolated aorta. *Br. J. Pharmacol.* **1997**, *121*, 711–716. [[CrossRef](#)] [[PubMed](#)]
44. Siciliano, R.; Barone, E.; Calabrese, V.; Rispoli, V.; Allan Butterfield, D.; Mancuso, C. Experimental research on nitric oxide and the therapy of Alzheimer disease: A challenging bridge. *CNS Neurol. Disord. Drug Targets* **2011**, *10*, 766–776. [[CrossRef](#)] [[PubMed](#)]
45. Kumar Nath, A.; Ghosh Dey, S. Dalton Transactions FRONTIER Simultaneous binding of heme and Cu with amyloid β peptides: Active site and reactivities. *Dalton Trans.* **2022**, *51*, 4986–4999. [[CrossRef](#)] [[PubMed](#)]
46. Sadleir Id, K.R.; Popovic, J.; Khatri, A.; Vassar, R. Oral nimodipine treatment has no effect on amyloid pathology or neuritic dystrophy in the 5XFAD mouse model of amyloidosis. *PLoS ONE* **2022**, *17*, e0263332. [[CrossRef](#)]
47. Yasar, S.; Corrada, M.; Brookmeyer, R.; Kawas, C. Calcium channel blockers and risk of AD: The Baltimore Longitudinal Study of Aging. *Neurobiol. Aging* **2005**, *26*, 157–163. [[CrossRef](#)]
48. Yasar, S.; Xia, J.; Yao, W.; Furberg, C.D.; Xue, Q.L.; Mercado, C.I.; Fitzpatrick, A.L.; Fried, L.P.; Kawas, C.H.; Sink, K.M.; et al. Antihypertensive drugs decrease risk of Alzheimer disease. *Neurology* **2013**, *81*, 896–903. [[CrossRef](#)] [[PubMed](#)]
49. Lawlor, B.; Segurado, R.; Kennelly, S.; Olde Rikkert, M.G.; Howard, R.; Pasquier, F.; Börjesson-Hanson, A.; Tsolaki, M.; Lucca, U.; Molloy, D.W.; et al. Nilvadipine in mild to moderate Alzheimer disease: A randomised controlled trial. *Fani Tsolaki-TagarakilD* **2018**, *25*, 39. [[CrossRef](#)]
50. Viel, A.T.; Buck, S.H. Kallikrein-kinin system mediated inflammation in Alzheimer's disease in vivo. *Curr. Alzheimer Res.* **2011**, *8*, 59–66. [[CrossRef](#)] [[PubMed](#)]
51. Asraf, K.; Torika, N.; Danon, A.; Fleisher-Berkovich, S. Involvement of the bradykinin B1 Receptor in microglial activation: In vitro and in vivo studies. *Front. Endocrinol. (Lausanne)* **2017**, *8*, 82. [[CrossRef](#)]
52. Chen, Z.L.; Singh, P.; Wong, J.; Horn, K.; Strickland, S.; Norris, E.H. An antibody against HK blocks Alzheimer's disease peptide β -amyloid-induced bradykinin release in human plasma. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 22921–22923. [[CrossRef](#)]
53. Dutra, R.C. Kinin receptors: Key regulators of autoimmunity. *Autoimmun. Rev.* **2017**, *16*, 192–207. [[CrossRef](#)]
54. Vivek Kumar, S.; Thakur Gurjeet, S. Navigating Alzheimer's Disease via Chronic Stress: The Role of Glucocorticoids. *Curr. Drug Targets* **2020**, *21*, 433–444. [[CrossRef](#)]
55. Gebre, A.K.; Altaye, B.M.; Atey, T.M.; Tuem, K.B.; Berhe, D.F. Targeting Renin-Angiotensin System Against Alzheimer's Disease. *Front. Pharmacol.* **2018**, *9*, 440. [[CrossRef](#)]
56. Singh, P.K.; Chen, Z.L.; Strickland, S.; Norris, E.H. Increased Contact System Activation in Mild Cognitive Impairment Patients with Impaired Short-Term Memory. *J. Alzheimers Dis.* **2020**, *77*, 59–65. [[CrossRef](#)] [[PubMed](#)]
57. Bitencourt, R.M.; de Souza, A.C.; Bicca, M.A.; Pamplona, F.A.; de Mello, N.; Passos, G.F.; Medeiros, R.; Takahashi, R.N.; Calixto, J.B.; Prediger, R.D. Blockade of hippocampal bradykinin B1 receptors improves spatial learning and memory deficits in middle-aged rats. *Behav. Brain Res.* **2017**, *316*, 74–81. [[CrossRef](#)]
58. Mugisho, O.O.; Robilliard, L.D.; Nicholson, L.F.B.; Graham, E.S.; O'Carroll, S.J. Bradykinin receptor-1 activation induces inflammation and increases the permeability of human brain microvascular endothelial cells. *Cell Biol. Int.* **2019**, *44*, 343–351. [[CrossRef](#)]

59. Zhong, K.L.; Chen, F.; Hong, H.; Ke, X.; Lv, Y.G.; Tang, S.S.; Zhu, Y.B. New views and possibilities of antidiabetic drugs in treating and/or preventing mild cognitive impairment and Alzheimer's Disease. *Metab. Brain Dis.* **2018**, *33*, 1009–1018. [[CrossRef](#)]
60. Ji, B.; Wang, Q.; Xue, Q.; Li, W.; Li, X.; Wu, Y. The Dual Role of Kinin/Kinin Receptors System in Alzheimer's Disease. *Front. Mol. Neurosci.* **2019**, *12*, 234. [[CrossRef](#)]
61. Vipin, A.; Ng, K.K.; Ji, F.; Shim, H.Y.; Lim, J.K.; Pasternak, O.; Zhou, J.H.; Alzheimer's Disease Neuroimaging Initiative. Amyloid burden accelerates white matter degradation in cognitively normal elderly individuals. *Hum. Brain Mapp.* **2019**, *40*, 2065. [[CrossRef](#)]
62. Zhang, X.; Yu, R.; Wang, H.; Zheng, R. Effects of rivastigmine hydrogen tartrate and donepezil hydrochloride on the cognitive function and mental behavior of patients with Alzheimer's disease. *Exp. Ther. Med.* **2020**, *20*, 1789–1795. [[CrossRef](#)]
63. Urmila, A.; Rashmi, P.; Nilam, G.; Subhash, B. Recent Advances in the Endogenous Brain Renin-Angiotensin System and Drugs Acting on It. *J. Renin Angiotensin Aldosterone Syst.* **2021**, *2021*, 9293553. [[CrossRef](#)] [[PubMed](#)]
64. Naffah-Mazzacoratti M da, G.; Gouveia, T.L.F.; Simões, P.S.R.; Perosa, S.R. What have we learned about the kallikrein-kinin and renin-angiotensin systems in neurological disorders? *World J. Biol. Chem.* **2014**, *5*, 130–140. [[CrossRef](#)] [[PubMed](#)]
65. Hajjar, I.; Brown, L.; Mack, W.J.; Chui, H. Impact of Angiotensin Receptor Blockers on Alzheimer Disease Neuropathology in a Large Brain Autopsy Series. *Arch. Neurol.* **2012**, *69*, 1632–1638. [[CrossRef](#)] [[PubMed](#)]

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