Table S1. Multivariate logistic regression to obtain the risk of AD from SBP and DBP and controlled by age, sex and antihypertensive intake.

Variables	Estimate	Standard Error	OR	Lower 95%	Upper 95%	P-value
(Intercept)	-11.167	2.739	0	0	0.003	<0.001
Age	0.161	0.032	1.174	1.105	1.255	<0.001
Sex (male)	-0.667	0.368	0.513	0.246	1.051	0.07
SBP	0.035	0.016	1.036	1.004	1.071	0.033
DBP	-0.033	0.024	0.967	0.921	1.013	0.166
Antihypertensive treatment	-0.07	0.373	0.933	0.446	1.941	0.852

DBP= Diastolic blood pressure; OR= Odds ratio; SBP= Systolic blood pressure.

Table S2. Association between t-tau/Aß42 ratio and sex, age, ARBs and ACEi drugs.

Variables	Estimate	Standard error	Lower- 95	Upper- 95	P-value
(Intercept)	-3.989	0.593	-5.157	-2.821	<0.001
Age	0.055	0.009	0.038	0.072	<0.001
Sex (male)	-0.226	0.1	-0.423	-0.029	0.025
ARBs, combinations	-0.334	0.142	-0.613	-0.055	0.019
ACEi, plain	0.19	0.162	-0.128	0.509	0.24
R Squared	0.1662				
Adj. R Squared	0.1541				

ACEi: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers.

Table S3. Relationship between renin-angiotensin-system- acting agents and Alzheimer's Disease biomarkers.

Step (Figure 4)	Relationship between renin-angiotensin-system (RAS)-acting agents and Alzheimer's Disease biomarkers	References
1. ACEi	Reduces Ang-II synthesis, enhancing acetylcholine and Ang-IV release	[1]
	Its chronic exposure may produce increased Aß42 levels in the brain	[2]
2- BK	Bradykinin receptors produce phospholipase C activation, which increases intracellular calcium mobilization, releases NO and prostaglandins and activate PKC, MAPK and NF-kB	[3-5]
3. B1R	Its expression is induced by MAPK, NF-kB and proinflammatory cytokines. Up-regulated in chronic inflammation	[4-11]

	Its expression and activation are linked to Aβ deposition and neuroinflammation in a mouse model of Alzheimer's disease	
4. B2R	B2R produces PKA as well, with which phospholipase C, phospholipase A2 and MAPK, can activate glutamate, NMDA and AMPA receptors, improving spatial memory. Up-regulated in acute inflammation.	[4,6,7,10]
5. XIIa factor	FXIIa activation of plasma prekallikrein leads to the release of bradykinin via cleavage of the intact form of HK	[4,12]
6. ARBs	Blocks AT1R, promoting the release of Ang II available to bind to Ang-IV, thereby facilitating memory and learning. It stimulates the PPARy, which is related to neuroprotection	[1]
	They are associated with a lower amyloid burden in non APOEe4+	[13]
7. AT1	It is naturally upregulated with ageing and its activation promotes M1 microglial phenotype activation, which releases TNF, IL-1ß, NO and ROS. It can impair cognitive function.	[14]
	Its activity is directly liked to inflammation, oxidation, neurotoxicity, and BBB damage	[15]
8. AT2	Linked to cell proliferation, differentiation, apoptosis, and regeneration of tissues	[16]
	Not detected on healthy microglia. Promotes M2 microglia phenotype, which produces anti-inflammatory cytokines	[14]
9. MasR	Neuroprotective effect. Enhances long-term potentiation	[14,16,17]
	Reduces oxidative stress: Increases NO and decreases mitochondrial respiration. Induces M2 microglia polarization, which enhances BDNF	[14]
10. Ang IV	Enhances cholinergic transmission and improves cognitive abilities.	[1,14,15]
11. ACE2	Its overexpression is associated with decreased activity of ACE1, Ang-II and AT1R expression, as well as decreased oxidative stress and neurofilament. It converts Aß43 into Aß42	[17]
12. ACE1	Increased ACE activity in patients with AD. Related to amyloid load and severity of AD	[2,17,18]
	It converts Aß42 into Aß40	[2,14,16,17]
13. Doxazosin	Doxazosin may reduce p-tau formation due to PI-3K/Akt-mediated inhibition of GSK-3 activity	[19]
14. NO	Neuroprotective at normal brain concentration. Its excess of its deficiency is associated with neurodegeneration and neuronal damage	[20]
15. GSK3ß	Angiotensin may activate GSK3ß and induce tau phosphorylation	[18]
	It may be activated by PS1 overexpression. Its overexpression is associated with disrupted islet ß cells and with tau hyperphosphorylation	[21]
16. CCB	Downregulate amyloid levels and slow its production	[22,23]
	Enhance cerebral vascularization	[24]

	Their effect on Aß clearance depends on their ability to facilitate Aß transcytosis. Drugs such as nimodipine or nitrendipine have this property	[25]

Aß= Amyloid beta peptide; ACEi= Angiotensin converting enzyme inhibitors; ACE1= Angiotensin converting enzyme 1; ACE2= Angiotensin converting enzyme 2; ARBs= Angiotensin receptor blockers; BDNF= brain-derived neurotrophic factor; BK= Bradykinin; AT1= Angiotensin 1 Receptor; AT2= Angiotensin 2 Receptor; B1R= Bradykinin 1 receptor; B2R= Bradykinin 2 receptor; CCB= Calcium channel blockers; GSK-3= Glycogen synthase kinase 3; HK= high molecular weight kininogen; MAPK= mitogen activated protein kinase; MasR= Mitochondrial Assembly Receptor; NF-kB= nuclear factor-kB; NO= nitric oxide; PKA= protein kinase A; PI-3K/Akt= Phosphatidylinositol 3-kinases/ protein kinase B; PKC= protein kinase isoforms; PPARy= peroxisome proliferator activated receptor gamma; ROS= Reactive Oxygen Species

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