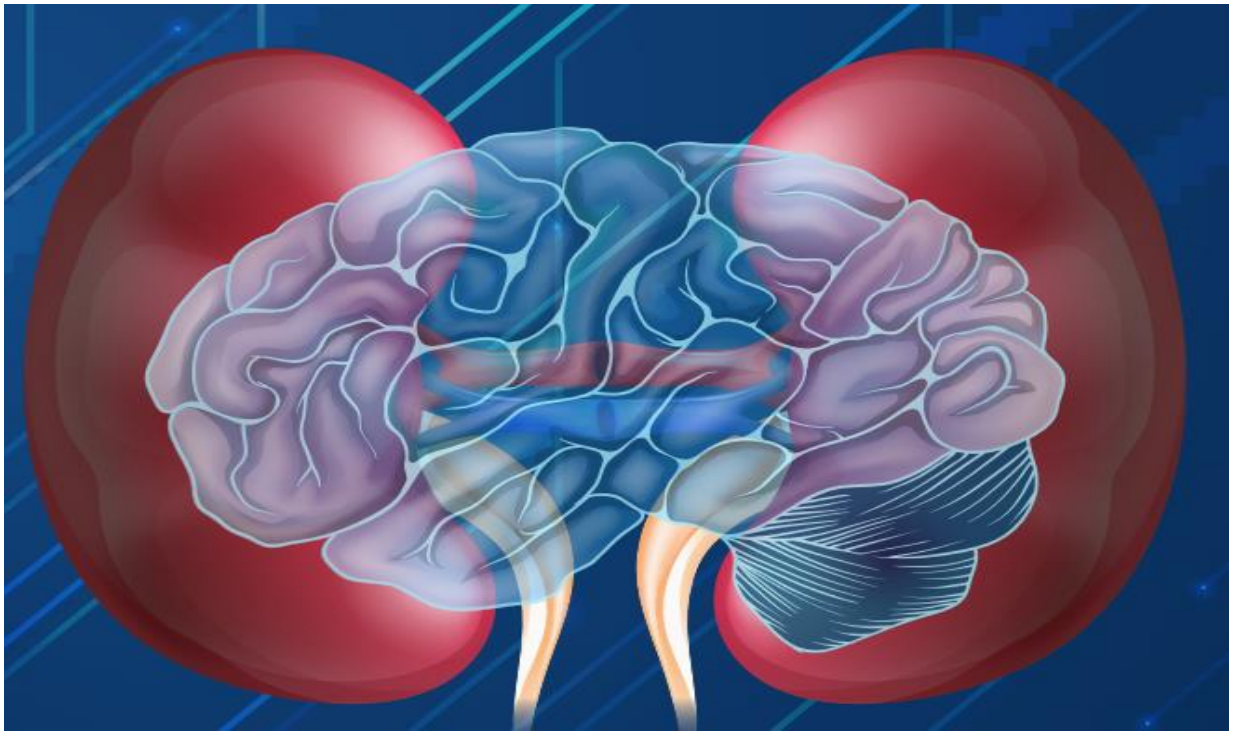
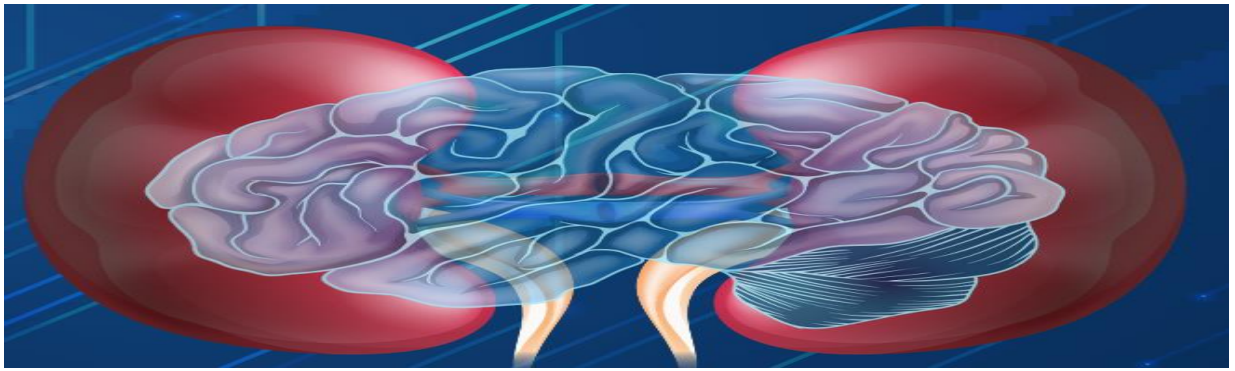


Διατήρηση της γνωσιακής λειτουργίας στον υπερτασικό ασθενή: φαρμακευτικές παρεμβάσεις

THE PREVENTION AND TREATMENT OF COGNITIVE DISORDERS

Includes the treatment of primary diseases That lead to cognitive decline

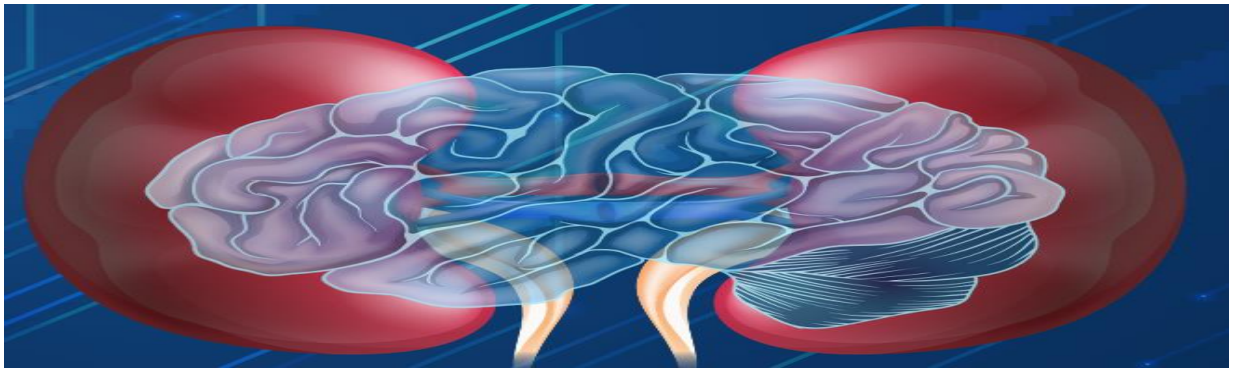
- ARTERIAL HYPERTENSION
- ATHEROSCLEROSIS,
- HEART FAILURE
- The control of neurological and psychopathological syndromes,
- The improvement of cerebral circulation and metabolism.



DRUGS OR STRATEGIES TO PREVENT COGNITIVE DYSFUNCTION

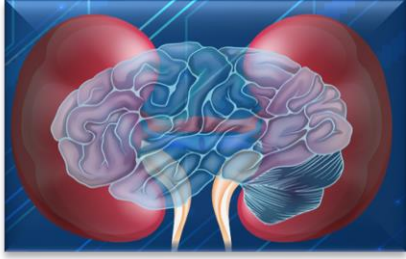
DRUGS TO PREVENT COGNITIVE DYSFUNCTION

- ANTIHYPERTENSIVE DRUGS
- HYPOLIPIDEMICS DRUGS
- SGLT2 INHIBITORS
- OTHERS



ANTIHYPERTENSIVE DRUGS TO PREVENT COGNITIVE DYSFUNCTION

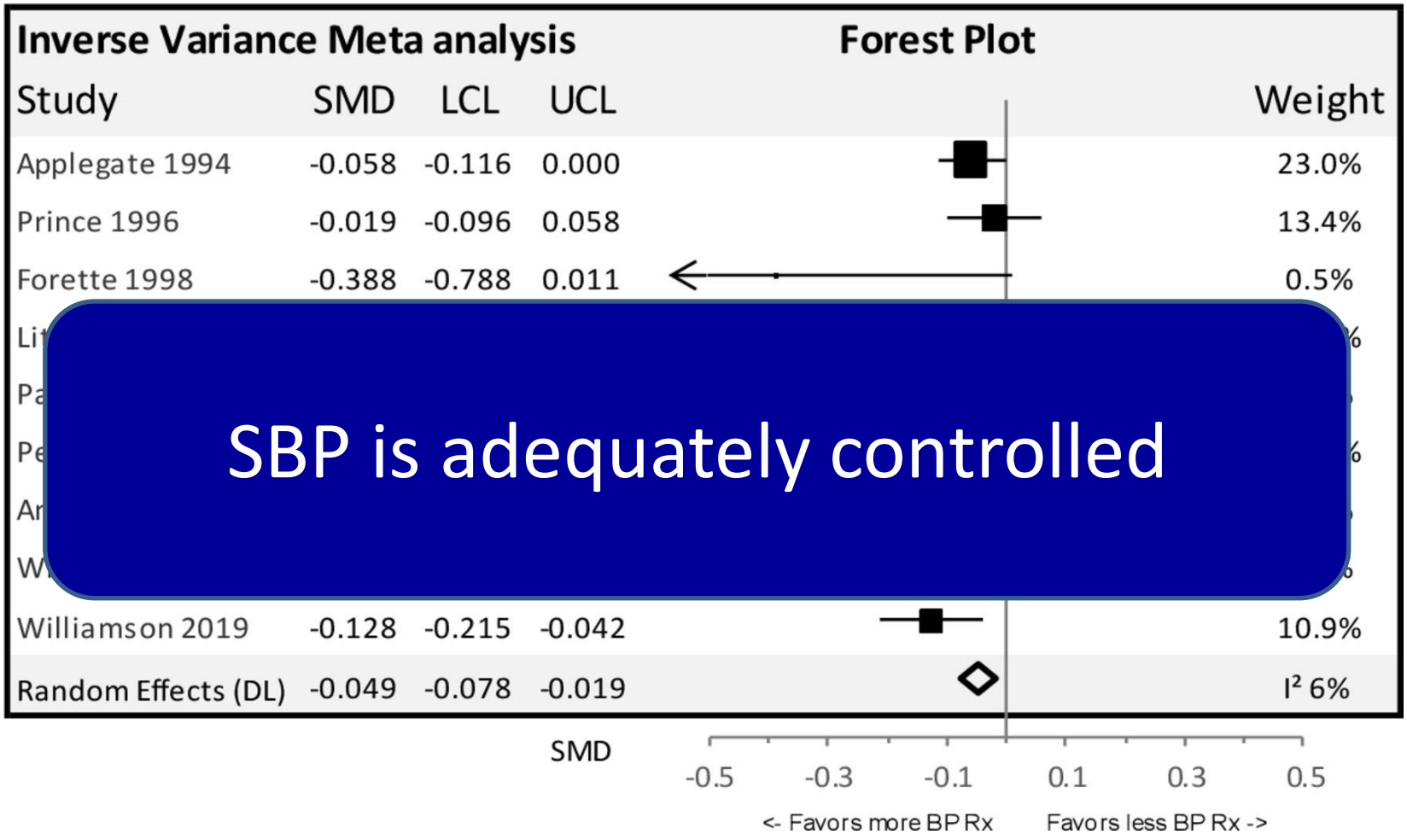
2023 ESH Guidelines for the management of arterial hypertension



The effects of antihypertensive drug class in late life to prevent cognitive impairmenthowever, remain unclear

Medication class may be less relevant if the SBP is not adequately controlled

Forest plot with the effect on cognition (SMD with 95% CI).



Aditi Gupta et al. BMJ Open 2020;10:e038971

BMJ Open

Reducing the Risk of Dementia
Efficacy of Long-Term Treatment of Hypertension

Rita Peila, PhD; Lon R. White, MD, MPH; Kamal Masaki, MD;
Helen Petrovitch, MD; Lenore J. Launer, PhD

Duration of Treatment With Antihypertensive Medication and Risk for Dementia, AD and VaD

	Dementia HR (95% CI)	AD HR (95% CI)	VaD HR (95% CI)
No.	1294	1251*	1205†
No. of cases	108	65	19
Duration of treatment (y)‡	0.94 (0.89–0.99)	0.96 (0.93–0.99)	0.94 (0.89–0.99)
Stratified by duration of treatment			
Never-treated hypertensives	1.00	1.00	1.00
Duration of treatment			
0–5 y	0.94 (0.52–1.72)	0.62 (0.27–1.43)	2.04 (0.6–6.9)
5–12 y	0.52 (0.24–1.09)	0.54 (0.21–1.36)	0.18 (0.10–1.71)
>12 y	0.40 (0.22–0.75)	0.35 (0.16–0.78)	0.32 (0.10–1.34)
Trend *P* value	0.001	0.014	0.009
Untreated normotensive	0.42 (0.20–0.89)	0.26 (0.10–0.66)	NA¶
Controlled BP§	0.45 (0.22–0.91)	0.24 (0.10–0.63)	0.42 (0.10–1.96)

In hypertensive men, the duration of the antihypertensive treatment is associated with a reduced risk for dementia and cognitive decline

Stroke. 2006;37:1165-1170.

Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack

Thomas P Zonneveld, Edo Richard, Mervyn DI Vergouwen, Paul J Nederkoorn, Rob J de Haan, Yvo BWEM Roos,

Myocardial infarction	34,747 (6 RCTs)	⊕⊕⊕⊕ High	RR 0.90 (0.72 to 1.11)	Study population 21 per 1000	2 fewer per 1000 (6 fewer to 2 more)
Vascular death	34,747 (6 RCTs)	⊕⊕⊕⊕ High	RR 0.85 (0.76 to 0.95)	Study population 47 per 1.000	7 fewer per 1000 (11 fewer to 2 fewer)
Death by any cause	35,110 (8 RCTs)	⊕⊕⊕⊖ Moderate[a]	RR 0.98 (0.91 to 1.05)	Study population 79 per 1000	2 fewer per 1000 (7 fewer to 4 more)
Dementia	6671 (2 RCTs)	⊕⊕⊕⊕ High	RR 0.88 (0.73 to 1.06)	Study population 67 per 1000	8 fewer per 1000 (18 fewer to 4 more)

https://doi.org/10.1002/14651858.CD007858.pub2

2023 ESH Guidelines for the management of arterial hypertension

The question if some antihypertensive drugs or strategies are better than others in preventing cognitive decline and dementia is still under debate

Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial

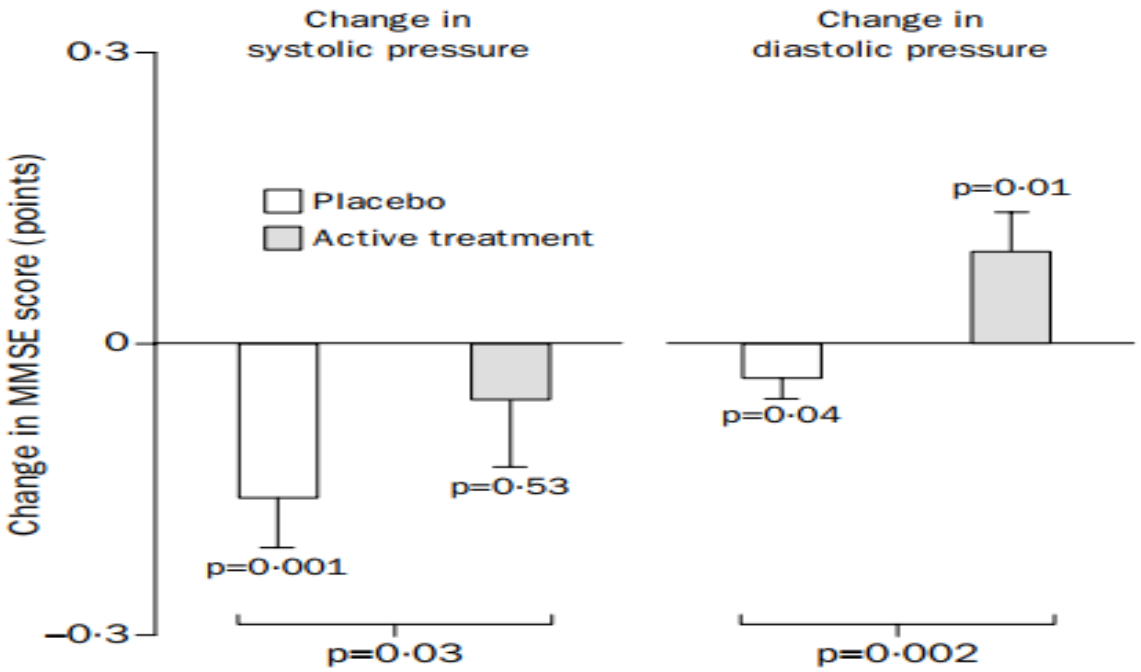


Figure 3: **Changes in MMSE score associated with mean decrease in systolic and diastolic blood pressure in placebo and active treatment groups**
Association sizes adjusted for sex, age, educational level, previous cardiovascular complications, antihypertensive treatment before enrolment, smoking, and alcohol consumption at randomisation.

In elderly patients with isolated systolic hypertension, **active treatment starting with the dihydropyridine calcium-channel blocker nitrendipine halved the rate of** dementia from 7·7 to 3·8 cases per 1000 patient-years.

In elderly people with isolated systolic hypertension, antihypertensive treatment was associated with a lower incidence of dementia.

Lancet 1998; 352: *1347–5*

ORIGINAL PAPERS: THERAPEUTIC ASPECTS

Relationship between antihypertensive drug therapy and cognitive function in elderly hypertensive patients with memory complaints

Hanon, Olivier[a]; Pequignot, Renaud[a]; Seux, Marie Laure[a]; Lenoir, Hermine[a]; Bune, Alexandra[b,c]; Rigaud, Anne Sophie[a]; Forette, Françoise[a]; Girerd, Xavier[d]

Treated hypertensive patients had better cognitive function than untreated patients

This association was observed independently of the cognitive status, both in normal, MCI, AD and VaD hypertensive patients.

The use of **CALCIUM ANTAGONISTS** was associated with a **decreased risk of cognitive impairment** and AD independently of the blood pressure level,

Journal of Hypertension 24(10):p 2101-2107, October 2006.

REVIEWS

Antihypertensive classes, cognitive decline and incidence of dementia

a network meta-analysis

Levi Marpillat, Natacha[a,b,c,d]; Macquin-Mavier, Isabelle[a,b]; Tropeano, Anne-Isabelle[e]; Bachoud-Levi, Anne-Catherine[a,b,d,f]; Maison, Patrick[a,b,c,d]

Author Information

Journal of Hypertension 31(6):p 1073-1082, June 2013. | **DOI:** 10.1097/HJH.0b013e3283603f53

A systematic review and included 19 randomized trials (18 515 individuals) and 11 studies (831 674 individuals)

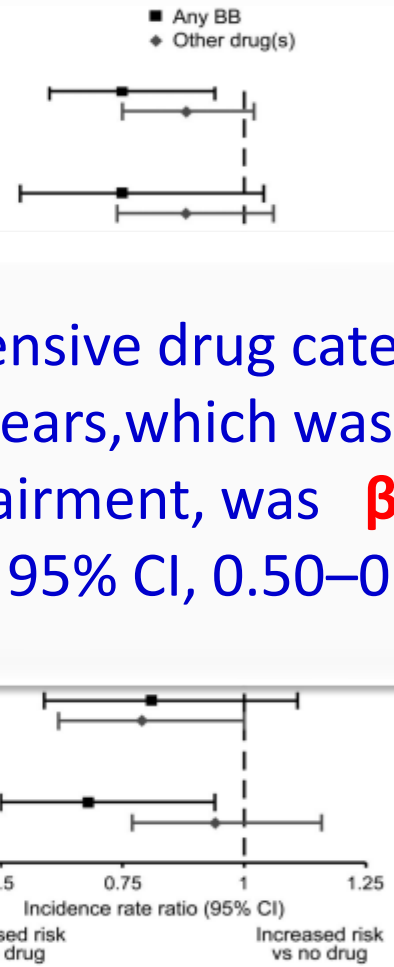
Antihypertensive treatment, regardless of the drug class, had benefits on overall cognition

These effects may differ between drug classes **WITH ARBS** possibly being the most effective.

Antihypertensive medication use and risk of cognitive impairment

The Honolulu-Asia Aging Study

	No. cases/ men	IRR (95% CI)
Use at baseline		
Any BB	108/335	0.75 (0.60-0.94)
Other drug(s)	363/956	0.88 (0.75-1.02)
Use at exams 4 and 6		
Any BB	45/112	0.75 (0.54-1.04)
Other drug(s)	220/464	0.88 (0.74-1.06)
Any BB	56/168	0.81 (0.59-1.11)
Other drug(s)	168/462	0.79 (0.62-1.00)
PP ≥70 mmHg		
Any BB	52/167	0.68 (0.50-0.94)
Other drug(s)	195/494	0.94 (0.77-1.16)



In HAAS, the only antihypertensive drug category when considered at mean age of 7years,which was associated with reduced cognitive impairment, was **β-blockers** (incidence rate ratio, 0.69; 95% CI, 0.50–0.94).187

: b-blocker use is associated with a lower risk of developing cognitive impairment in elderly Japanese American men. (incidence rate ratio, 0.69; 95% CI, 0.50–0.94).

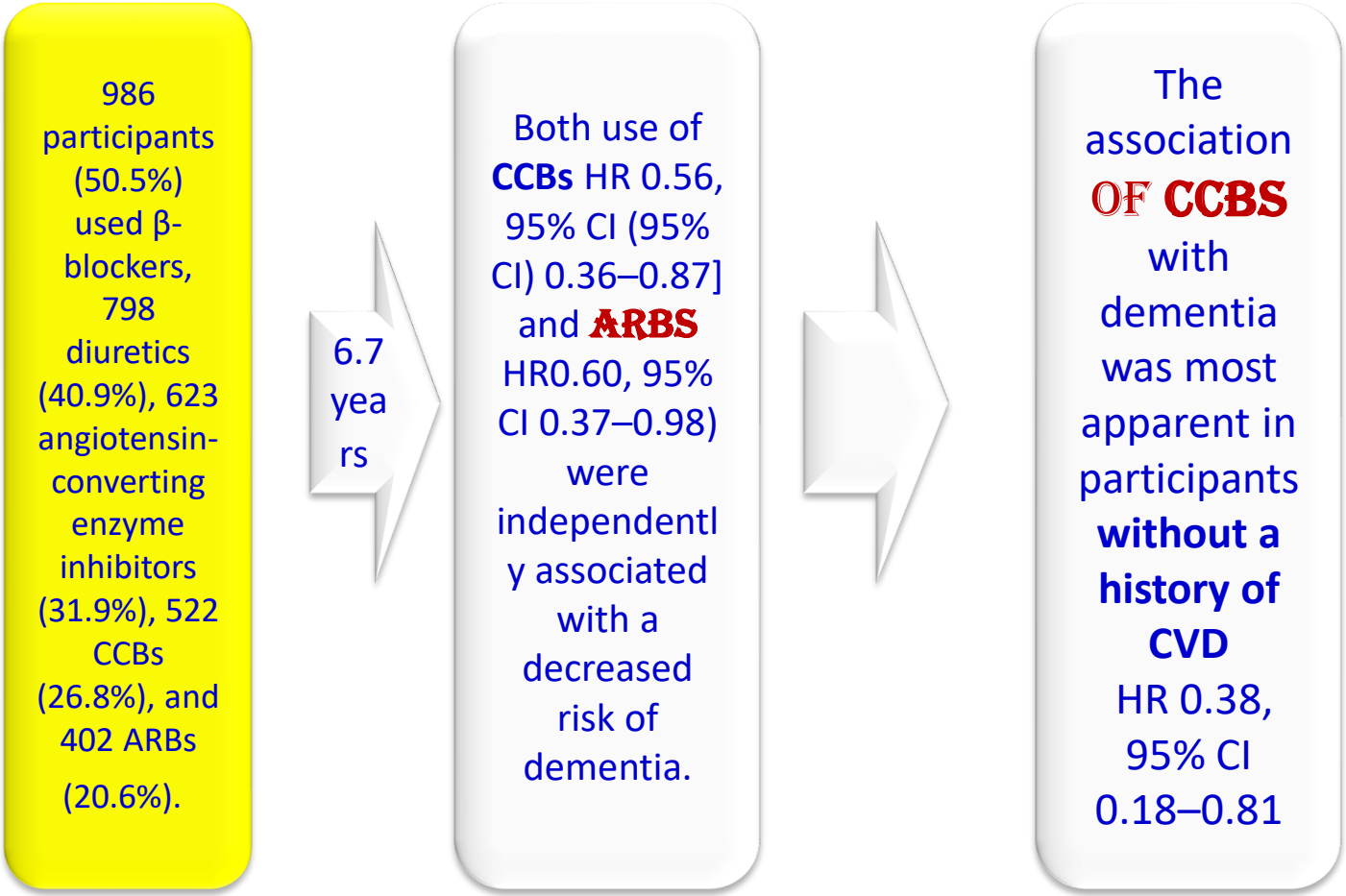
Neurology 2013;81:888–895

Lower dementia risk with different classes of antihypertensive medication in older patients

van Middelaar, Tessa[a,b]; van Vught, Lonneke A.[c]; van Charante, Eric P. Moll[c]; Eurelings, Lisa S.M.[a]; Ligthart, Suzanne A.[c]; van Dalen, Jan W.[a]; van den Born, Bert Jan H.[d]; Richard, Edo[a,b]; van Gool, Willem A.[a]

Author Information

Journal of Hypertension 35(10):p 2095-2101, October 2017. | **DOI:** 10.1097/HJH.0000000000001411



Original Article

OPEN

Antihypertensive medication classes and the risk of dementia over a decade of follow-up

Jakob L. Schroevers[a,*], Esme Eggink[a,*], Marieke P. Hoevenaar-Blom[b], Jan Willem Van Dalen[c], Tessa Van Middelaar[d], Willem A. Van Gool[b], Edo Richard[b,c], and Eric P. Moll Van Charante[a,b]

		Total (*N* = 1907)	ACEi (*N* = 620)	ARB (*N* = 390)	Beta-blocker (*N* = 958)	CCB (*N* = 512)	Diuretic (*N* = 974)	Dihydropyridine CCB (*N* = 399)	ATII-stimulating AHM (*N* = 1180)
Sociodemographic									
Age (years)	Mean ± SD [Range]	74.5 ± 2.5 [69–80]	74.5 ± 2.5 [69–80]	74.3 ± 2.5 [69–79]	74.4 ± 2.5 [69–80]	74.5 ± 2.5 [69–80]	74.5 ± 2.5 [69–80]	74.4 ± 2.5 [69–80]	74.4 ± 2.5 [69–80]
Sex (female)	*N* (%)	1027 (53.9)	280 (45.2)	219 (56.2)	492 (51.4)	273 (53.3)	591 (60.7)	215 (53.9)	682 (57.8)
MMSE	Median [IQR]	28 [27–29]	28 [27–29]	29 [27–29]	28 [27–29]	29 [27–29]	29 [27–29]	29 [27–29]	29 [27–29]
Cardiovascular risk factors and medication use									
CVD history (yes)	N (%)	947 (49.7)	315 (50.8)	184 (47.2)	589 (61.5)	289 (56.4)	438 (45.0)	204 (51.1)	517 (43.8)
DM history (yes)	N (%)	501 (26.3)	233 (37.6)	110 (28.2)	240 (25.1)	154 (30.1)	301 (30.9)	126 (31.6)	332 (28.1)
SBP (mmHg)	Mean ± SD [Range]	156.2 ± 21.5 [100–232.5]	156.6 ± 21.9 [100–233]	156.5 ± 23.1 [103–222]	156.6 ± 22.5 [100–233]	155.8 ± 20.4 [109–218]	155.9 ± 21.5 [100–233]	157.5 ± 20.3 [109–218]	157.7 ± 21.0 [101–233]
DBP (mmHg)	Mean ± SD [Range]	81.4 ± 11.2 [50–131]	81.4 ± 11.9 [52–131]	81.5 ± 11.2 [55–118]	80.9 ± 11.4 [50–131]	79.4 ± 10.4 [52–125]	81.3 ± 10.8 [52–119]	79.7 ± 10.4 [52–125]	81.6 ± 10.9 [52–125]
BMI (kg/m^2)	Mean ± SD	28.4 ± 4.3	28.2 ± 4.1	29.1 ± 4.6	28.3 ± 4.0	28.5 ± 4.2	28.9 ± 4.5	28.6 ± 4.1	28.7 ± 4.4
LDL (mg/dl)	Mean ± SD	112.0 ± 38.6	108.1 ± 34.8	112.0 ± 38.6	108.1 ± 34.8	108.1 ± 34.8	112.0 ± 38.6	108.1 ± 34.8	112.0 ± 38.6
Current smoking (yes)	*N* (%)	232 (12.2)	79 (12.7)	40 (10.3)	121 (12.6)	66 (12.9)	117 (12.0)	52 (13.0)	141 (11.9)
Physically active (yes)	*N* (%)	1565 (82.1)	493 (79.5)	321 (82.3)	797 (83.2)	414 (80.9)	778 (79.9)	325 (81.5)	974 (82.5)
Number of AHM	Median [IQR]	2 [2–3]	2 [2–3]	2 [2–3]	2 [1–3]	2 [2–3]	2 [2–3]	2 [2–3]	2 [2–3]

dividual participants are represented in different classes of antihypertensive medication when they use combination therapy. Data are presented as numbers (percentage), mean ± SD, median (IQR) or ranges. Physical activity was self-ported and defined according to WHO criteria. ACEi, angiotensin-converting enzyme inhibitor; AHM, antihypertensive medication; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CVD, rdiovascular disease; DM, diabetes mellitus; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination.

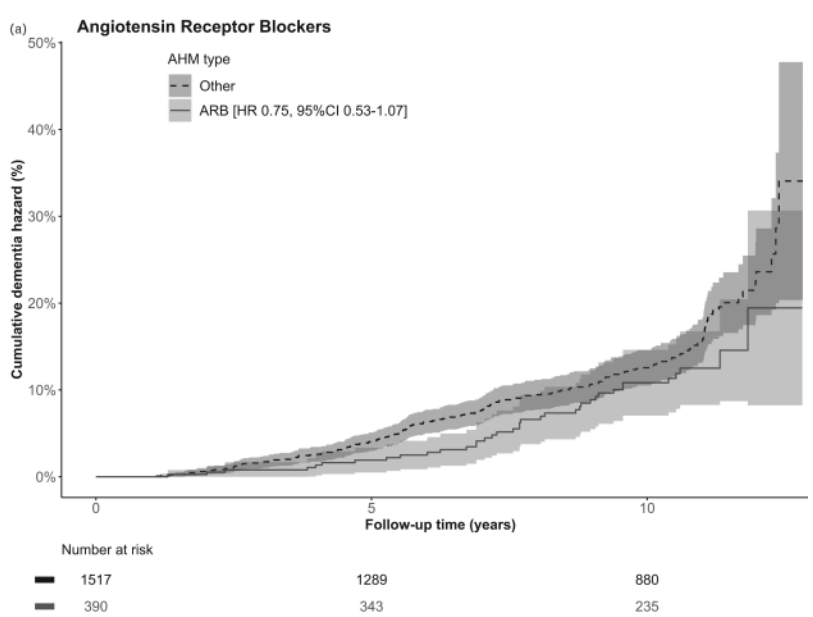
Journal of Hypertension 2023, 41:262–270

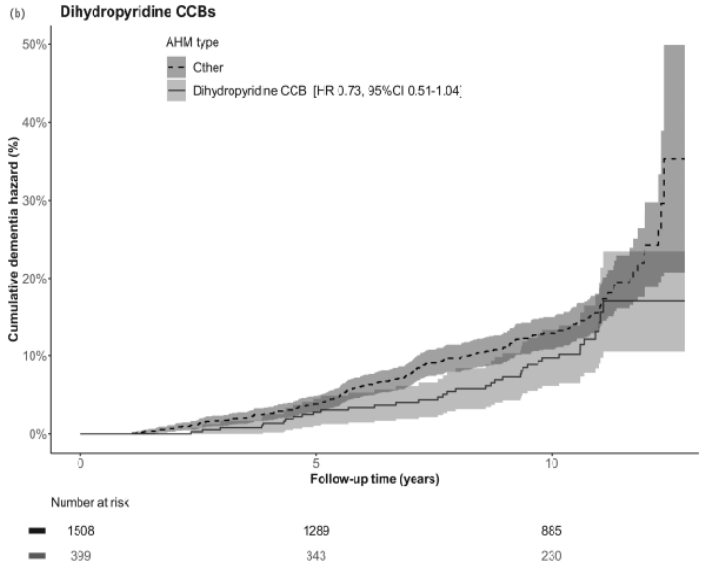
Original Article

OPEN

Antihypertensive medication classes and the risk of dementia over a decade of follow-up

Jakob L. Schroevers[a,*], Esme Eggink[a,*], Marieke P. Hoevenaar-Blom[b], Jan Willem Van Dalen[c], Tessa Van Middelaar[d], Willem A. Van Gool[b], Edo Richard[b,c], and Eric P. Moll Van Charante[a,b]





Use of **ARBs, dihydropyridine CCBs and ATII-stimulating antihypertensives** is associated with lower dementia risk over a decade, although associations attenuate over time. Apart from methodological aspects, differential effects of antihypertensive medication classes on incident dementia may in part be temporary, or decrease with ageing.

Journal of Hypertension 2023, 41:262–270

The Association Between Hypertension and Cognitive Impairment, and the Role of Antihypertensive Medications: A Literature Review

Nupur Mishra [1] , Devyani Mohan [2] , Sehrish Fuad [1] , Deepak M. Basavanagowda [3] , Zaid A. Alrashid [4] , Arveen

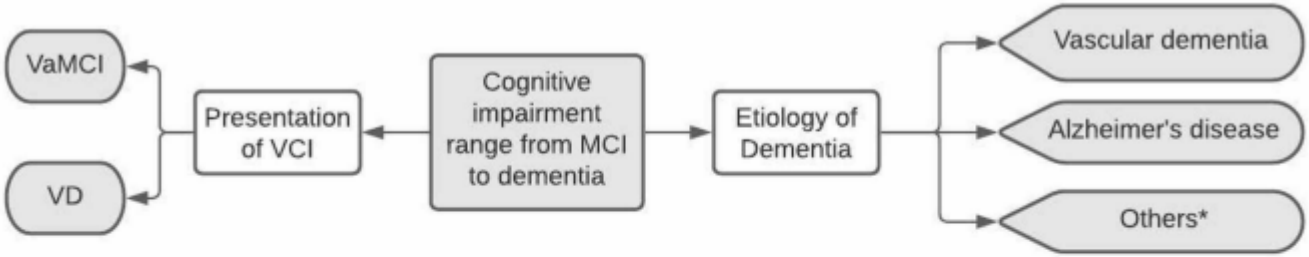
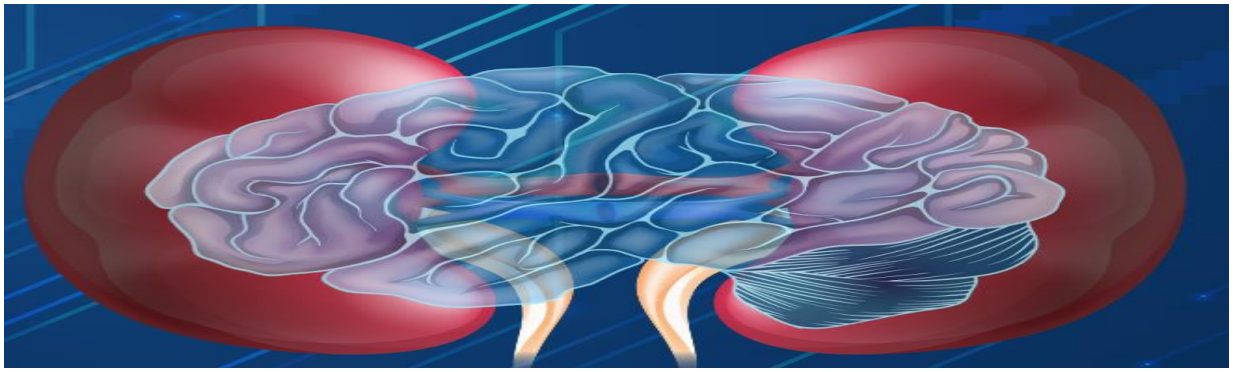


FIGURE 2: Overview of different etiologies of dementia and the range of presentation of vascular cognitive impairment

*Other causes include frontotemporal dementia, Lewy body dementia, pseudodementia, HIV-associated dementia, etc.

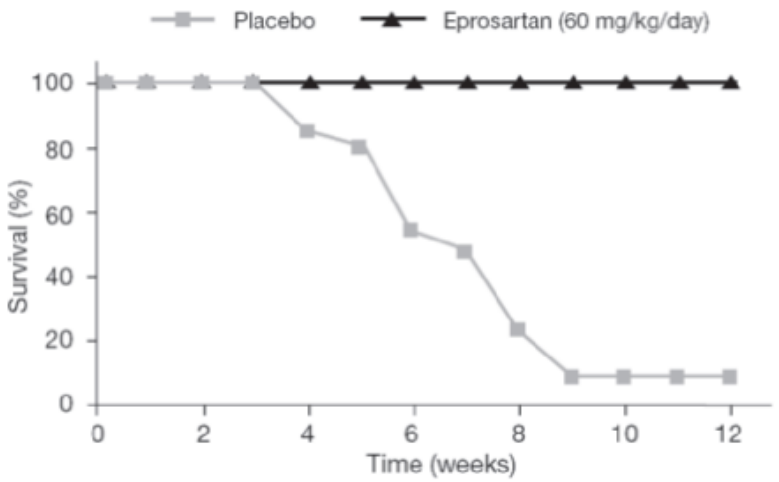
MCI: mild cognitive impairment, VCI: vascular cognitive impairment, VaMCI: vascular mild cognitive impairment, VD: vascular dementia

The STUDIES DID NOT SUGGEST A SUPERIORITY OF ANY SPECIFIC AHM CLASS to prevent CI. Further research on optimal hypertension treatment goals to prevent cognitive impairment and dementia is recommended.



DRUGS OR STRATEGIES THE ROLE OF RAS BLOCKERS TO PREVENT COGNITIVE DYSFUNCTION

Observational Study on Cognitive function And systolic blood pressure Reduction (OSCAR): preliminary analysis of 6-month data from > 10 000 patients and review of the literature



Parameter	Change with eprosartan
Absolute change in BP from baseline to 6 months:	
SBP	–26.6 mmHg
DBP	–12.6 mmHg
Response to treatment from baseline to 6 months:	
Percentage of normalised patients*	61%
Percentage of responders† at final visit	91%
Absolute change in MMSE from baseline to 6 months:	
Overall population	0.9 ($p < 0.001$)
Elderly patients (70–80 years):	1.3
Adverse events:	
≥1 AE thought to be related to study treatment	1.4% ($n = 154$)
Serious AE	0.1% ($n = 7$)
Withdrawal due to AE	1.0% ($n = 114$)

Changes in study endpoints with eprosartan at 6 months compared with baseline in patients in the OSCAR study

Eprosartan-treated rats on a high-fat, high-salt
diet exhibited zero mortality at week 12 compared with placebo-treated animals.

CuRRent MediCAl ReSeARCh And OpiniOn®
VOl. 23, Suppl. 5, 2007, S13–S18

Associations of Anti-Hypertensive Treatments with Alzheimer's Disease, Vascular Dementia, and Other Dementias

Associations of ACE-Is with dementia after sequentially excluding all prescriptions between one to eight years prior to diagnosis (lags)

Lag years[a]	Exposed		Unexposed		ORs (95% CI)	*p*-value
	Cases	Controls	Cases	Controls		
Probable or possible Alzheimer's disease						
0	1,959	14,794	3,606	21,631	0.79 (0.74–0.83)	<0.001
1	1,826	13,229	3,614	21,781	0.83 (0.78–0.88)	<0.001
2	1,624	11,730	3,514	21,571	0.85 (0.79–0.91)	<0.001
3	1,428	10,265	3,437	21,080	0.86 (0.80–0.92)	<0.001
4	1,239	8,832	3,288	20,366	0.88 (0.82–0.94)	<0.001
5	1,068	7,392	3,105	19,530	0.92 (0.85–0.99)	0.03
6	883	6,071	2,897	18,114	0.92 (0.84–1.00)	0.04
7	723	4,881	2,638	16,585	0.94 (0.86–1.03)	0.17
8	586	3,942	2,360	14,791	0.94 (0.85–1.04)	0.22
Probable vascular dementia						
0	841	14,794	1,222	21,631	0.82 (0.75–0.91)	<0.001
1	800	13,229	1,227	21,781	0.89 (0.81–0.98)	0.02
2	711	11,730	1,215	21,571	0.90 (0.82–1.00)	0.05
3	619	10,265	1,198	21,080	0.90 (0.81–1.00)	0.05
4	536	8,832	1,183	20,366	0.90 (0.81–1.01)	0.06
5	445	7,392	1,145	19,530	0.89 (0.79–1.00)	0.06
6	373	6,071	1,055	18,114	0.92 (0.81–1.04)	0.20
7	312	4,881	974	16,585	0.95 (0.83–1.09)	0.50
8	254	3,942	897	14,791	0.94 (0.81–1.09)	0.45

Journal of Alzheimer's Disease 26 **(2014)** 699–708DOI 10.3233/JAD-2011-110347

Associations of Anti-Hypertensive Treatments with Alzheimer's Disease, Vascular Dementia, and Other Dementias

Associations of ARBs with dementia after sequentially excluding all prescriptions between one to eight years prior to diagnosis (lags)

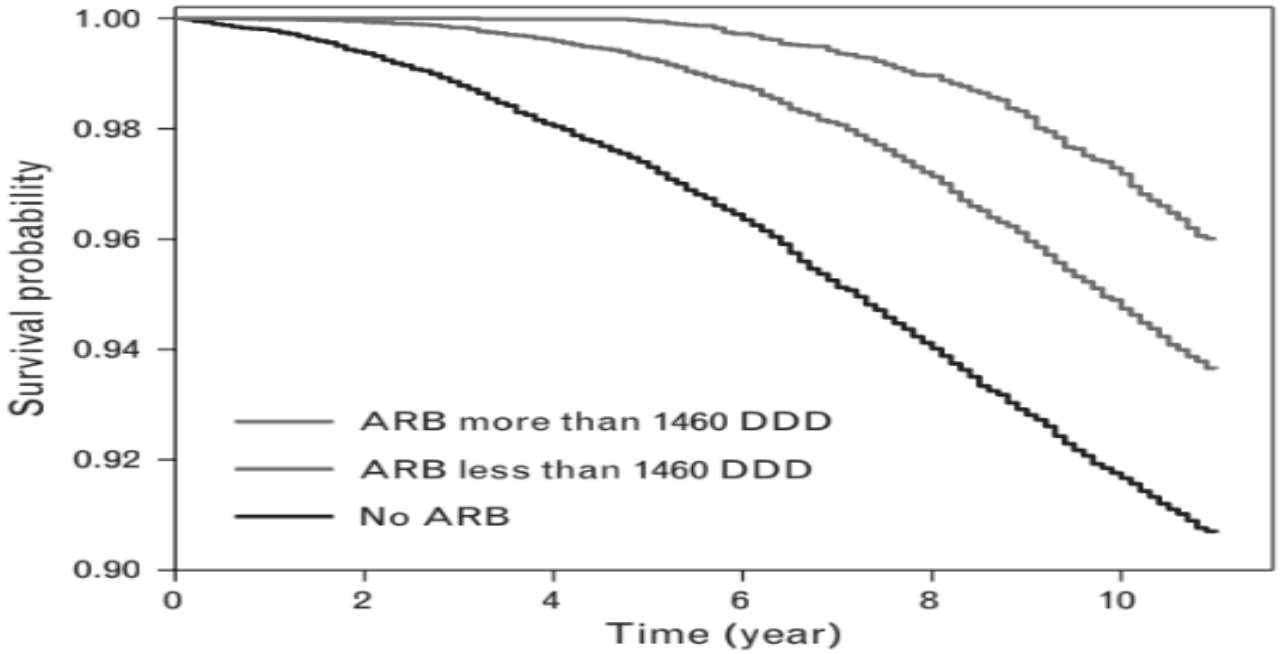
Lag years[a]	Exposed		Unexposed		ORs (95% CI)	*p*-value
	Cases	Controls	Cases	Controls		
Probable or possible Alzheimer's disease						
0	232	2,741	3,606	21,631	0.49 (0.43–0.56)	<0.001
1	209	2,271	3,614	21,781	0.54 (0.47–0.63)	<0.001
2	176	1,789	3,514	21,571	0.59 (0.50–0.69)	<0.001
3	132	1,378	3,437	21,080	0.57 (0.48–0.69)	<0.001
4	90	979	3,288	20,366	0.56 (0.45–0.70)	<0.001
5	58	657	3,105	19,530	0.54 (0.41–0.71)	<0.001
6	34	418	2,897	18,114	0.50 (0.35–0.71)	<0.001
7	18	240	2,638	16,585	0.46 (0.28–0.75)	0.002
8	9	128	2,360	14,791	0.43 (0.22–0.84)	0.01
Probable vascular dementia						
0	123	2,741	1,222	21,631	0.70 (0.57–0.85)	<0.001
1	114	2,271	1,227	21,781	0.79 (0.65–0.97)	0.02
2	100	1,789	1,215	21,571	0.88 (0.71–1.09)	0.25
3	83	1,378	1,198	21,080	0.93 (0.74–1.18)	0.57
4	64	979	1,183	20,366	1.00 (0.77–1.31)	0.98
5	42	657	1,145	19,530	0.96 (0.69–1.33)	0.81
6	25	418	1,055	18,114	0.92 (0.61–1.39)	0.70
7	11	240	974	16,585	0.69 (0.37–1.27)	0.23
8	6	128	897	14,791	0.63 (0.28–1.46)	0.28

There were inverse dose-response relationships between ARBs and ACE-Is with AD (both ptrend < 0.01). The inverse association of ACE-Is with AD diminished when using longer time lags but the ARB-AD association persisted.
Patients with AD were around half as likely to be prescribed ARBs.

Journal of Alzheimer's Disease 26 (2014) 699–708DOI 10.3233/JAD-2011-110347

Angiotension receptor blockers reduce the risk of dementia

Wei-Che Chiu[a,b,c], Wen-Chao Ho[d], Meng-Hung Lin[d], Hsiu-Hao Lee[a,e], Yu-Chi Yeh[b,f], Jung-Der Wang[a,g], Pau-Chung Chen[a,h,i], Health Data Analysis in Taiwan (hDATa) Research Group

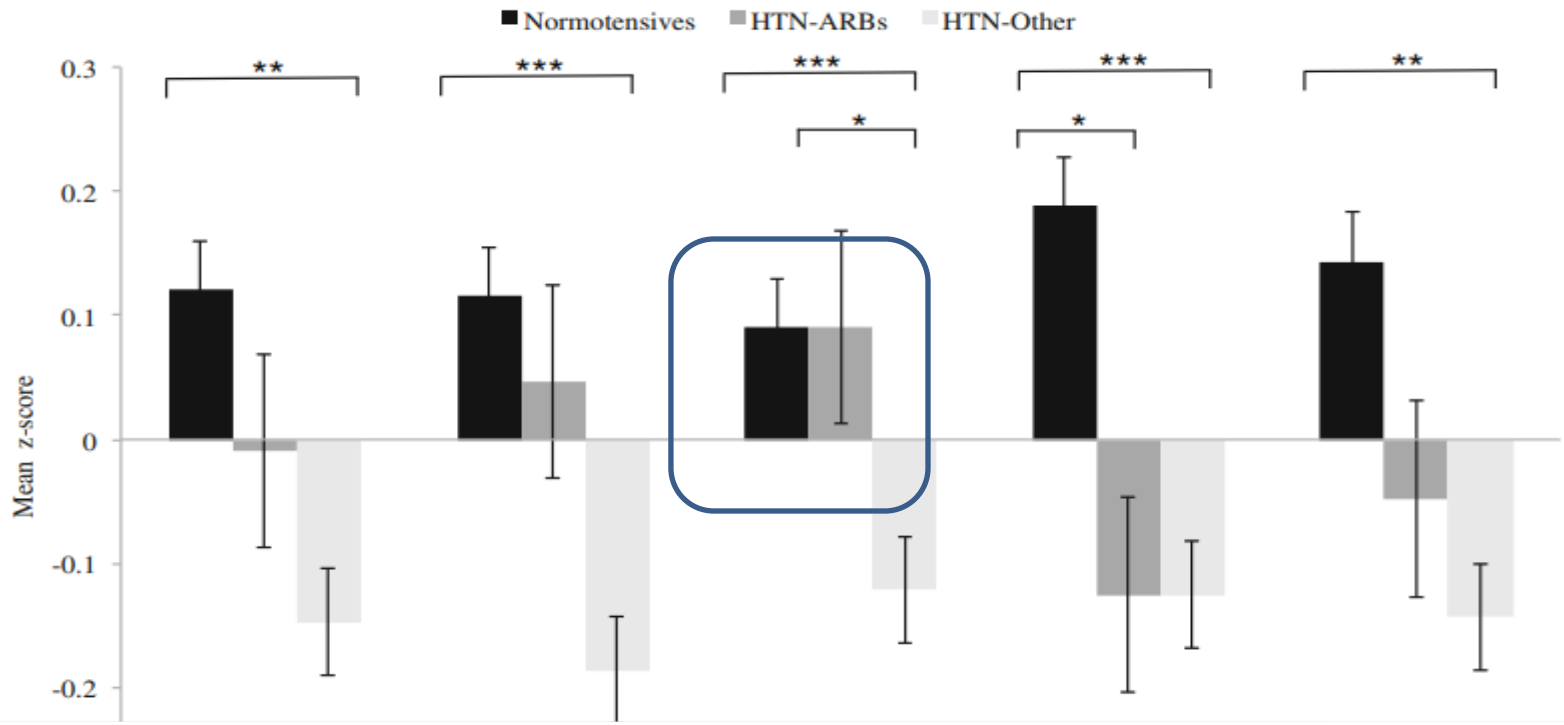


Kaplan–Meier curves of the cumulative incidence of dementia without adjustment in the groups with more than 4-year DDD (n 1⁄4 6726), less than 4-year
DDD (n 1⁄4 17 805) and without ARB (n 1⁄4 24 531) therapy in 11-year ARB cohort

J Hypertens 32:938–947 **2014**

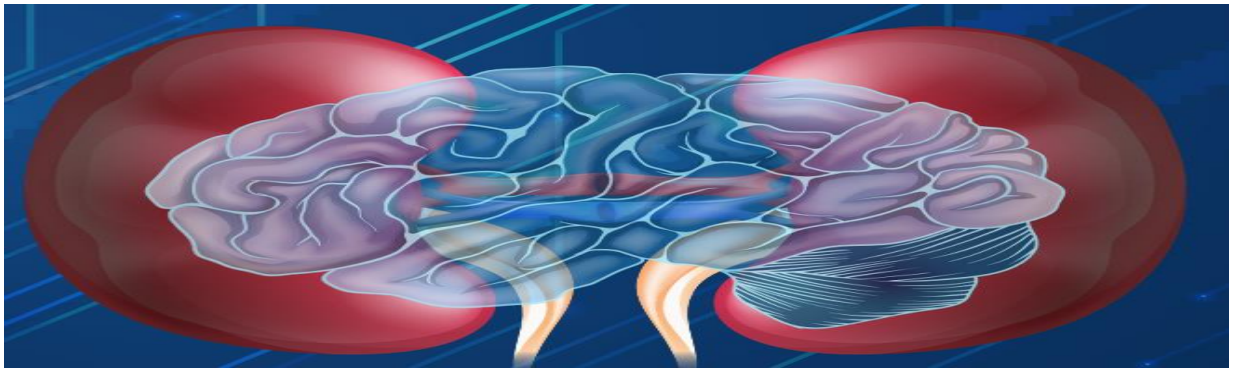
Memory is preserved in older adults taking AT1 receptor blockers

Jean K. Ho*, Daniel A. Nation* for the Alzheimer's Disease Neuroimaging Initiative



The participants who took other antihypertensive drugs that were not angiotensin II receptor blockers (HTN-Other) performed worse on tests of memory, attention, and executive function than normotensive subjects. However, angiotensin II receptor blocker users (HTN-ARBs) did not differ from normotensive subjects on memory function and demonstrated better recognition memory than those taking other antihypertensive medications. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. RAVLT Rey Auditory Verbal Learning Test

Ho and Nation Alzheimer's Research & Therapy **(2017) 9:33**



THE FENOMENON
OF AT1 BLOCKERS

RAS localization in the brain

Angiotensinogen, the main precursor of all angiotensin peptides, is mostly produced within astrocytes (90%) in nearly all regions of the brain. It is then secreted and converted to several neuroactive peptides

Angiotensinogen and renin are
co-expressed in several areas of the brain,
including the CA1–3 region of the hippocampus

Ageing Research Reviews 77 (2022)

RAS localization in the brain

RAS system is composed of three essential axis that exert beneficial effects –
ACE 1/Ang II/AT2R;
ACE 2/Ang (1- 7)/MasR;
Ang IV/ AT4R(IRAP) –
and one that is
responsible for the deleterious effects – ACE 1/Ang II/AT1R.

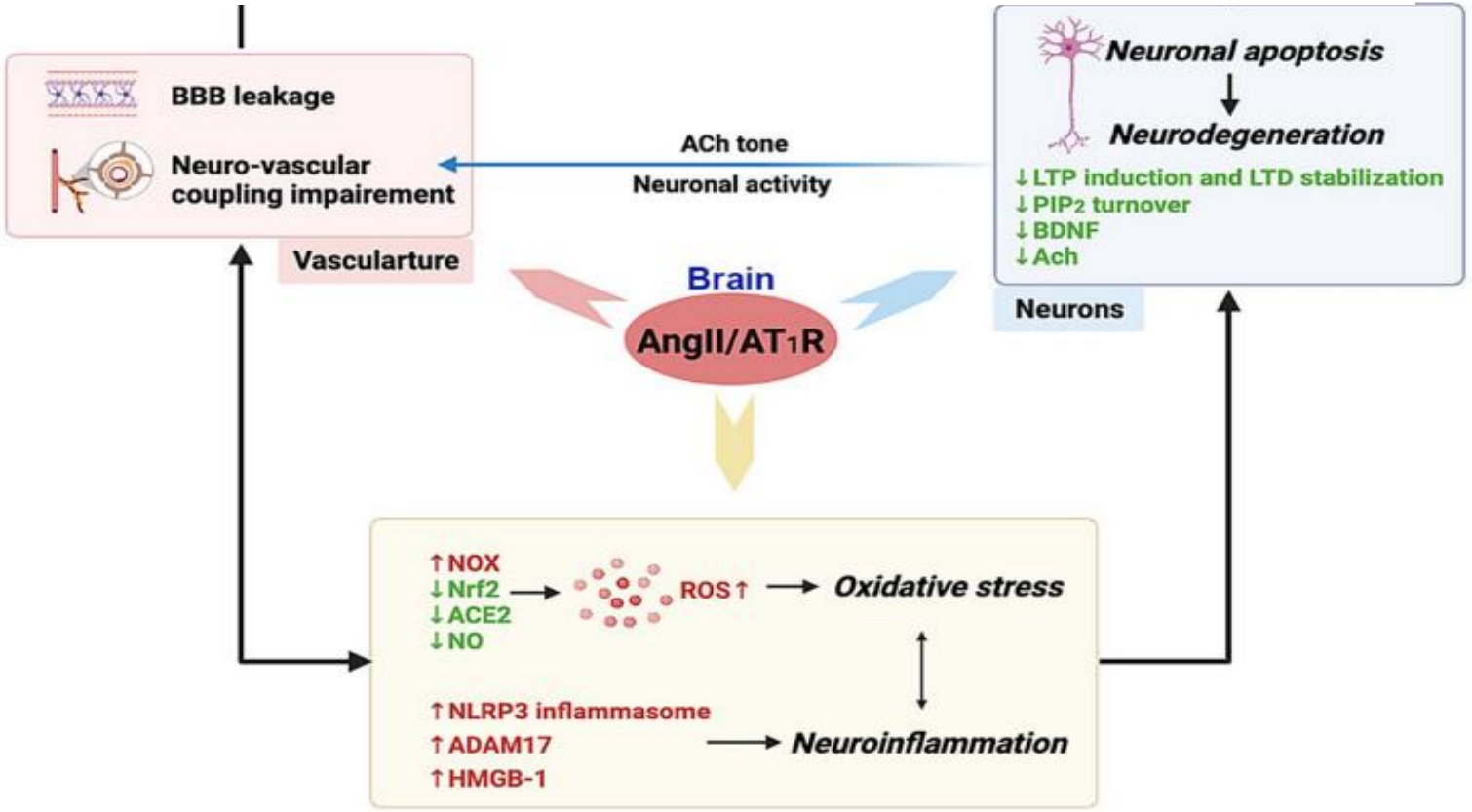
They complement each other in perfect harmony and their relevance on learning and memory

The ACE 1/Ang II/AT1R has been linked to the deleterious effects of the systemic and brain RAS.
In fact, it is thought to be responsible for anncrement of the oxidative stress, neuroinflammation, BBB permeability,
astrocytes dysfunction and a decrease in CBF (Mogi et al., 2012).

Ageing Research Reviews 77 (2022)

AT1 Receptors: Their Actions from Hypertension to Cognitive Impairment

Hanxue Wu[1] · Qi Sun[2] · Shenglan Yuan[1] · Jiawei Wang[1] · Fanni Li[2] · Hongli Gao[1] · Xingjuan Chen[3] · Rui Yang[1] · Jiaxi Xu[1]



Schematic illustration of how brain AT1R promotes neurodegeneration and cognitive impairment. Neurodegeneration and vascular dysfunction are not independent of each other. For one thing, they share similar signaling pathways, as shown in the yellow bubble. For another, during hypertension, vascular dysfunction could be a key trigger for neurodegeneration, while changed acetylcholine (Ach) tone and neuronal activity would further compromise the functional hyperemia Possible roles of AT1R in etiology of cognitiveimpairment

AT1 Receptors: Their Actions from Hypertension to Cognitive Impairment

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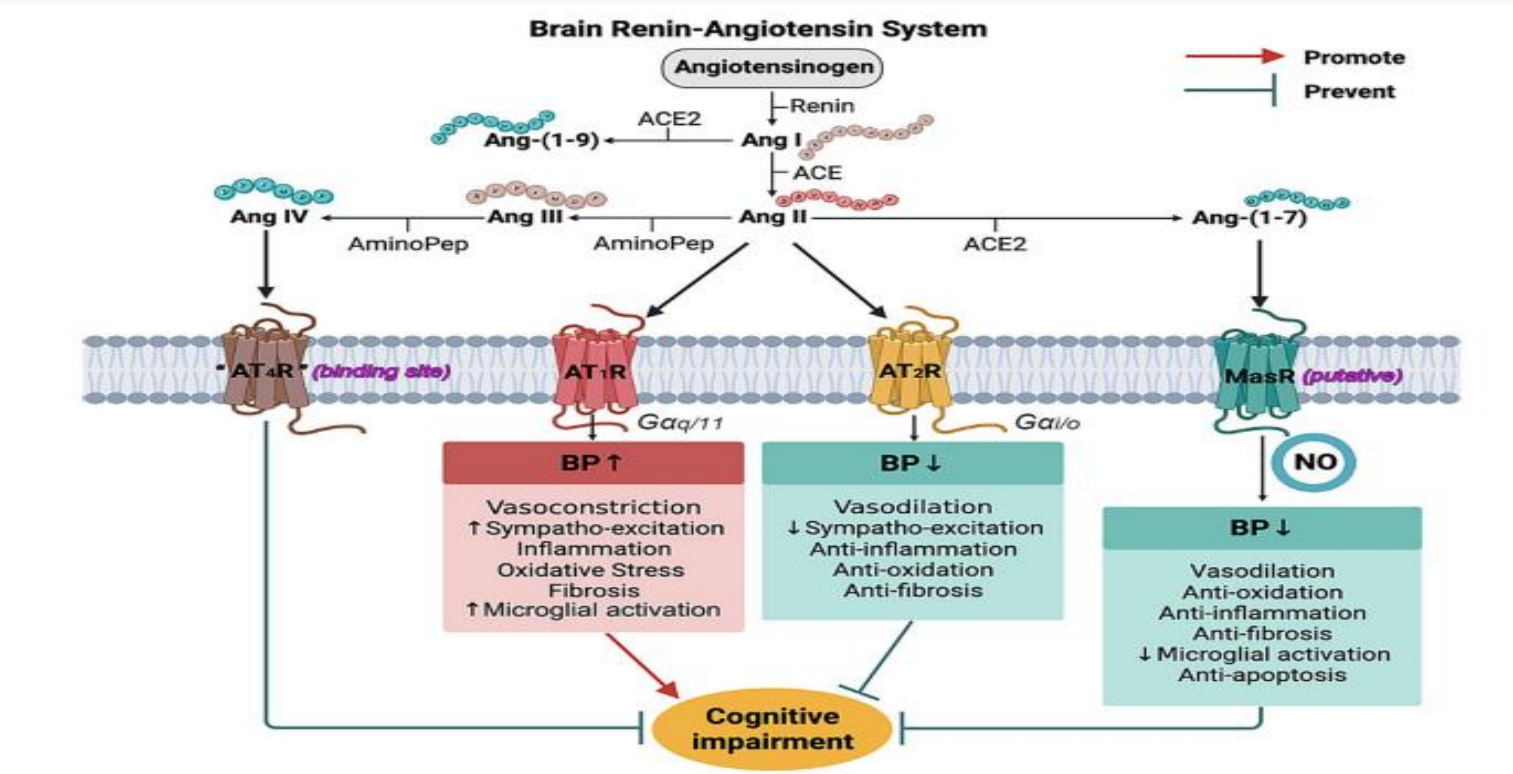


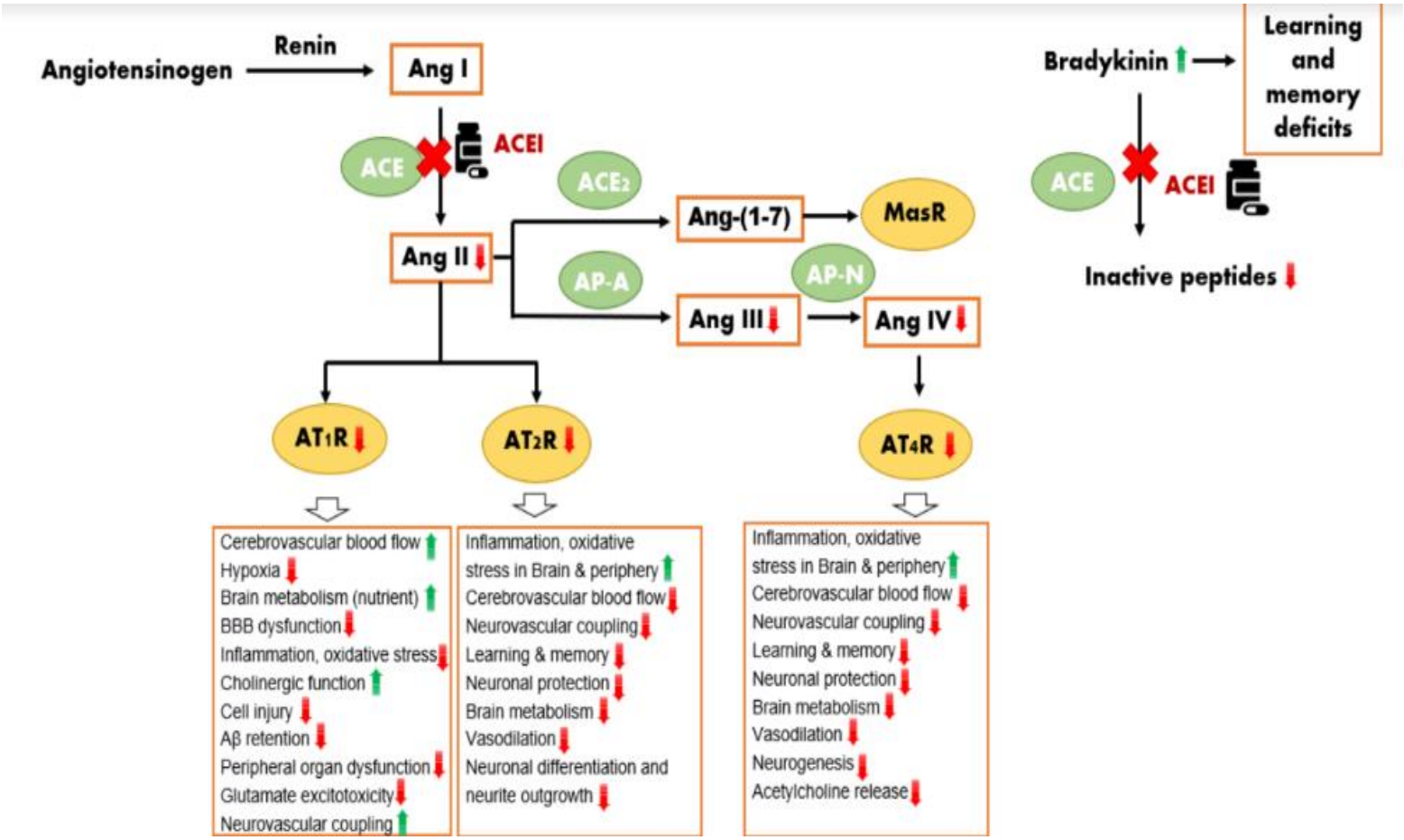
In general, Ang-II/AT1R pathway induces deleterious impact on cognitive function, promoting cognitive impairment, while the others exhibit protective efects at diferent levels

ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (M ERNST, SECTION EDITOR)

Angiotensin Receptor Blockers and Cognition: a Scoping Review

Zhen Zhou[1,2] · Suzanne G. Orchard[1] · Mark R. Nelson[2] · Michelle A. Fravel[3] · Michael E. Ernst[3,4]

Accepted: 21 August 2023



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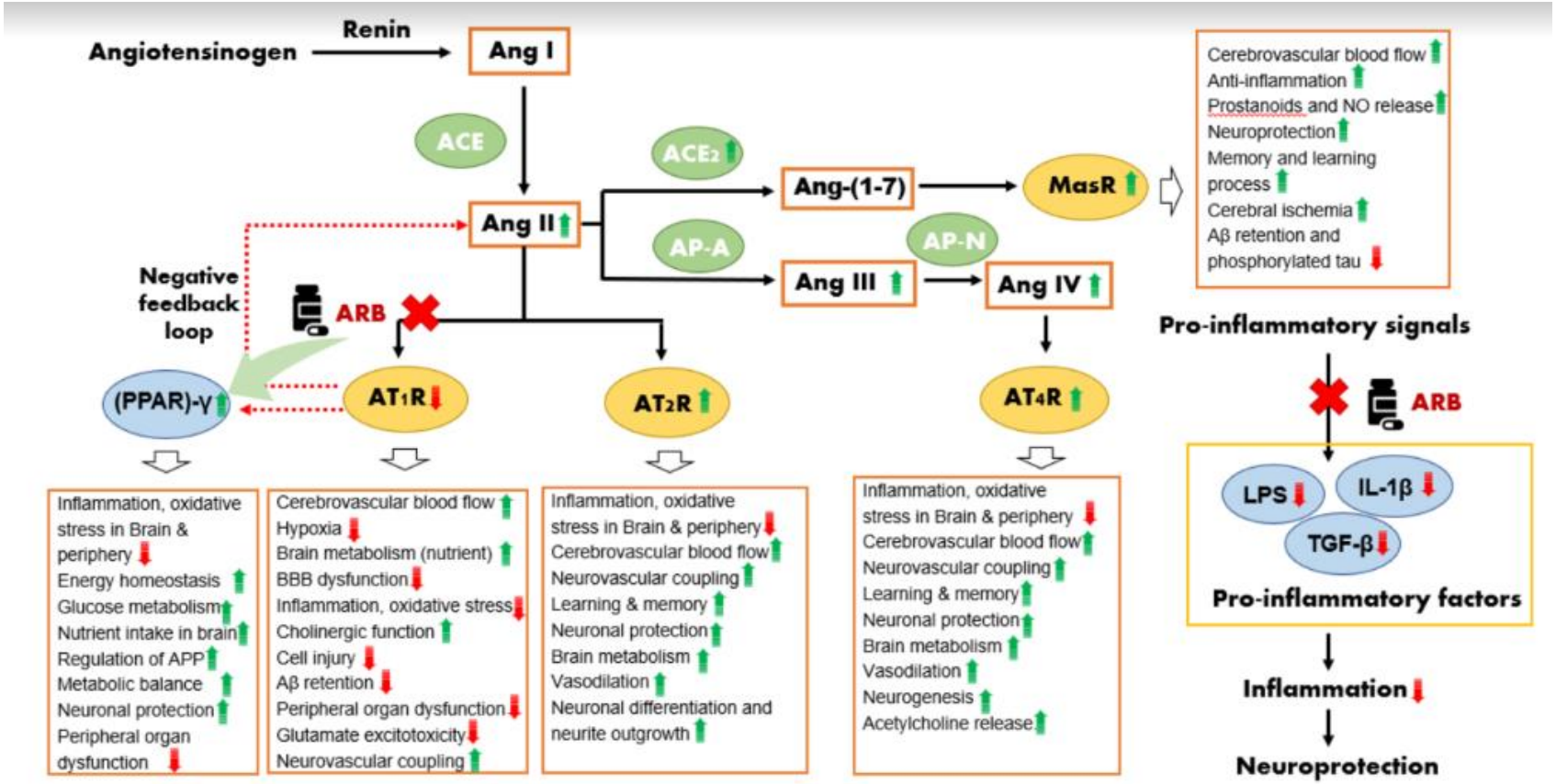

AT1 Receptors: Their Actions from Hypertension to Cognitive Impairment

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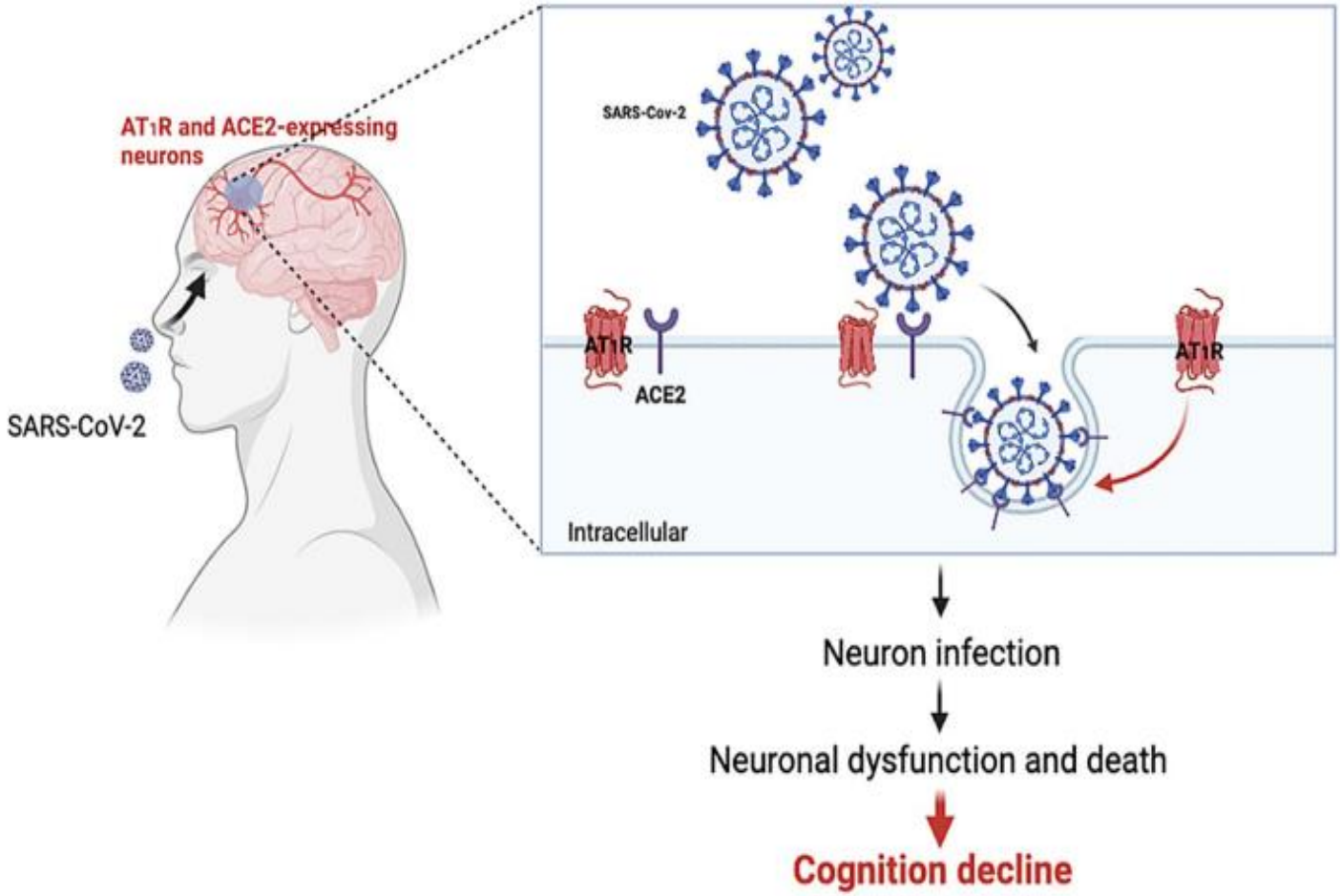
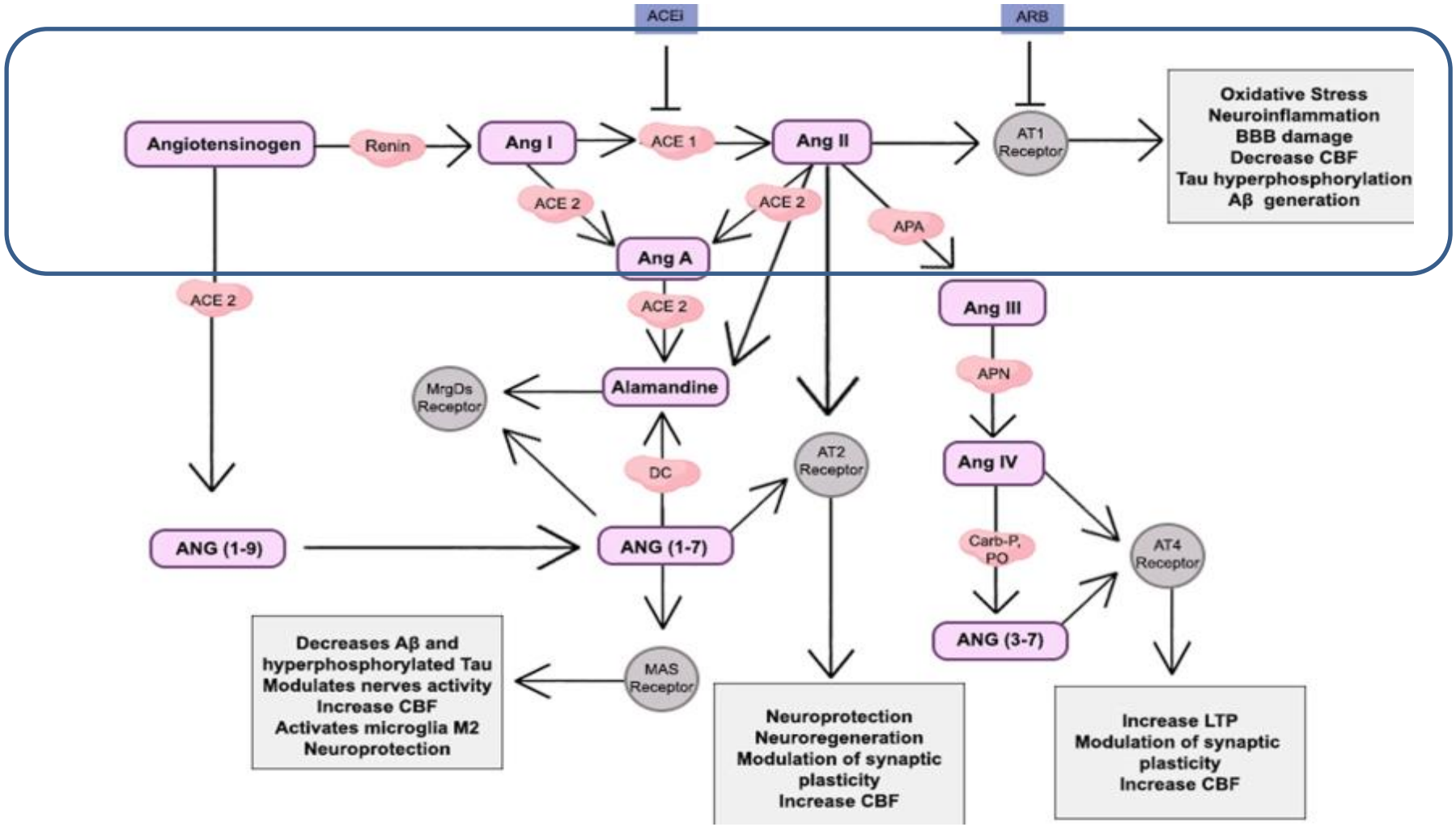


Summary of the RAS system, including the four main axis- ACE 1/Ang II/AT1R; ACE 1/ Ang II/AT2R; ACE 2/Ang(1- 7)/MasR; Ang IV/ AT4R(IRAP).



Aβ, amyloid β Ang,angiotensin; ACE, angiotensin convertingenzyme; ACEI, ACE inhibitor; AT1R; angiotensin type 1 receptor; APA, aminopeptidase A;APN, aminopeptidase N; BBB, blood-brain barrier; Carb-P; carboxypeptidase P; CBF, cerebral blood flow; DC, decarboxylase; LTP, long-termpotentiation; PO, prolyl oligopeptidase.

Ageing Research Reviews 77 (2022)

THE BENEFITS ARE PRIMARILY ATTRIBUTED TO THE ARB'S EFFECT

Modulating the renin-angiotensin

- ❖inhibiting the Ang II/AT1R pathway
- ❖activating the Ang II/AT2R,
- ❖activating Ang IV/AT4R,
- ❖activating and Ang-(1–7)/MasR

PLEIOTROPIC NEUROCOGNITIVE BENEFITS

- ❖ reduced β-amyloid accumulation abnormal hyperphosphorylation of tau,
- ❖ ameliorated brain hypofusion,
- ❖reduced neuroinflammation and synaptic dysfunction,
- ❖better neurotoxin clearing,
- ❖blood–brain barrier function restoration.

ACEIS EFFECT COUNTERBALANCE THE POTENTIAL BENEFITS

- ❖inhibit AT1R

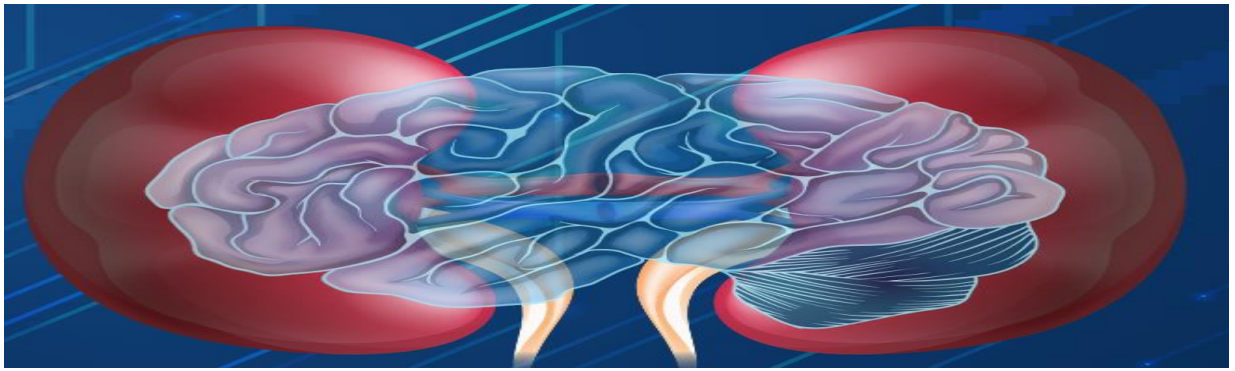
- ❖Smultaneously lower Ang II
- ❖Block the Ang II/AT2R pathway
- ❖Block the Ang IV/AT4R pathways

.

EFFECTS OF ARBS ON IN VITRO ALZHEIMER'S DISEASE MODELS

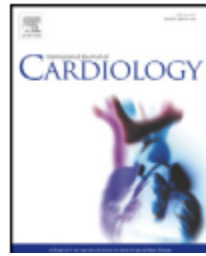
Telmisartan-	BV2 microglial cells	5 μ M	-ELISA for quantification of TNF-α, IL-1β and IL-10;	↓IL-1 β and TNF-α; ↑ IL-10; Inhibited NF-κB; ↓ Akt and ERK phosphorylation;	(Wang et al., 2019)
	-BV2 microglial cells- Primary rat neonatal glial cells and microglia	1 and 5 μ M	-Griess reaction to measure supernatant nitrite concentration as an indicator of NO production; -ELISA for quantification of TNF-α and IL-1β;	↓NO, iNOS, IL-1 β and TNF-α;	(Torika et al., 2016a)
	CGCs	1–20 μM	-Measurement of LDH activity (cell viability); -TUNEL and DAPI staining to determine apoptotic morphology of CGCs; -Apoptotic DNA fragmentation assay; -Measurement of caspase-3 activity; -Quantitative real-time PCR to determine gene expression; -Electrophoretic mobility shift assay; -Western blotting to quantify β-Actin, pAkt, Akt, pGSK-3β, GSK-3β, pERK1/2, ERK1/2, MAP-2;	↓ LDH release; ↓ TUNEL stained cells and caspase-3 levels; ↓IL-1 β and COX-2 mRNA expression; ↑ Gene expression of PPAR-γ; ↓ Akt dephosphorylation, GSK-3 β dephosphorylation and ERK1/2 phosphorylation;	(Wang et al., 2014a)
	SK-N-SH neuroblastoma cell line	1–10 μM	-Real-time PCR to determine gene expression; -Western blotting to determine NFκ B-p65 nuclear translocation; -Measurement of reactive oxygen species; -NADPH oxidase activity assay; -Ang II measurement by enzyme immunoassay;	↓COX-2 mRNA and PGE_2 release; ↓ NOX-4 expression, ROS production and NADPH oxidase activity; ↓ JNK and c-Jun phosphorylation; No effect on either p38 MAPK and ERK1/2 phosphorylation; No effect on IκB-α mRNA expression or the NFκ B-p65 protein nuclear translocation;	(Pang et al., 2012)
	-C6 Rat astrocytoma cell line- BV2 murine microglial cell line;	1 pM, 1 nM, and 1 μM	-MTT assay to measure cell viability; -ELISA to quantify TNFα, IL-10, Ang II; -to measure supernatant nitrite concentration as an indicator of NO production; -Fluorescent dye DCF-DA to quantify ROS;	No evidence of cytotoxicity; Ameliorated LPS-induced gliosis (all concentrations); Prevented morphological alterations (all concentrations); ↓ AT1R levels but not Ang II levels;	(Bhat et al., 2016)

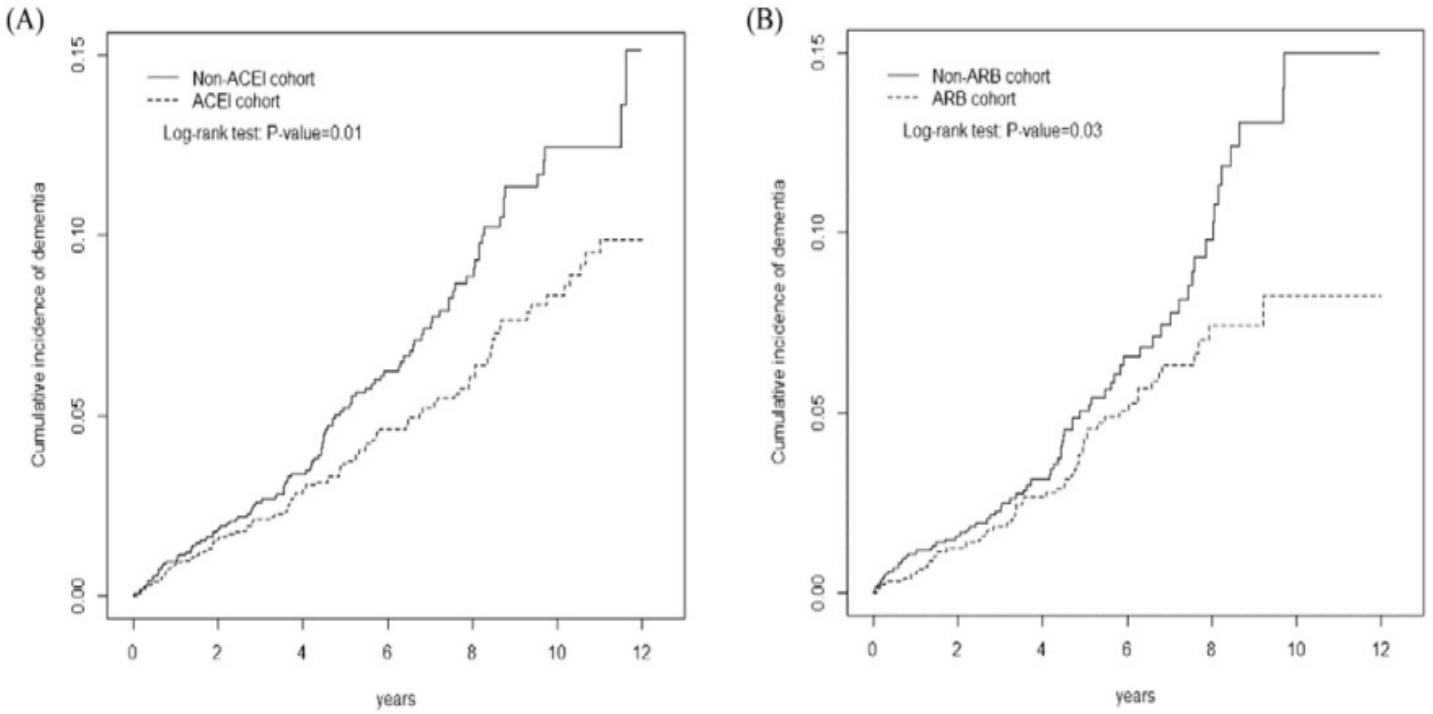
Ageing Research Reviews 77 (2022)



CLINICAL TRIALS

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers reduced dementia risk in patients with diabetes mellitus and hypertension





ACEIs and ARBs may effectively prevent all-cause dementia, particularly VD, in patients with type 2DM and hypertension. Moreover, compared with ACEIs, ARBs appear to be more advantageous in dementia prevention

International Journal of Cardiology 220 (2016) 462–466

Neuroprotective effect of angiotensin II receptor blockers on the risk of incident Alzheimer'sdisease: A nationwide population-based cohort study

RAS inhibitor type and blood–brain barrier (BBB) permeability on the risk of AD

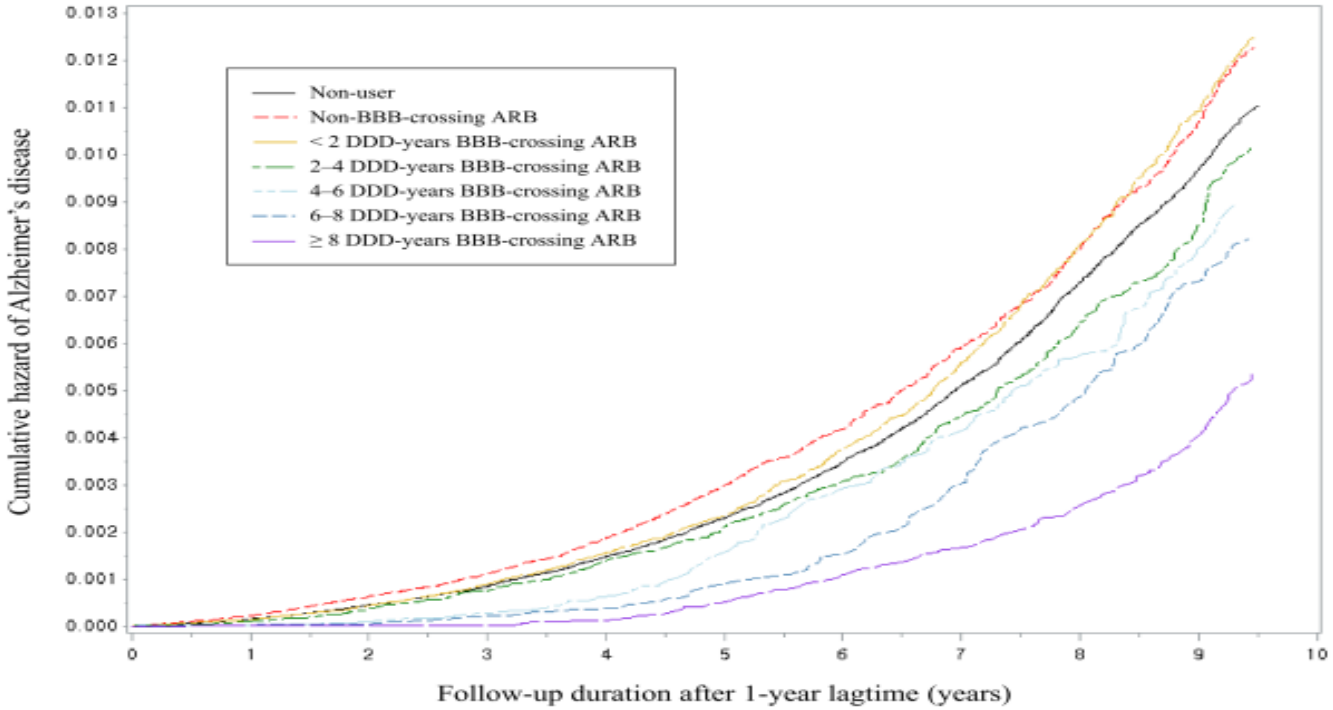


FIGURE 2
Kaplan–Meier curves for the cumulative hazard of Alzheimer's disease with a 2 defined daily dose (DDD)-year interval by blood–brain barrier (BBB)-crossing angiotensin II receptor blockers (ARBs).

Long-term use of BBB-crossing ARBs significantly reduced the risk of AD development. The finding may provide valuable insight into diseasemodifying drug options for preventing AD in patients with cardiovascular diseases

Front. Aging Neurosci. 15:1137197.doi: 10.3389/fnagi.2023.1137197

- Poor **BBB-crossing ACEIs** (alacepril, benazepril, cilazapril, enalapril, imidapril, moexipril, and quinapril),
- **BBB-crossing ACEIs** (captopril, delapril, fosinopril, lisinopril, perindopril, ramipril, temocapril, trandolapril, and zofenopril),
- poor BBB-crossing ARBs (eprosartan, irbesartan, losartan, and olmesartan),
- **BBB-crossing ARBs** (azilsartan, candesartan, fimasartan, telmisartan, and valsartan).

DRUGS TO PREVENT COGNITIVE DYSFUNCTION

ANTIHYPERTENSIVE DRUGS

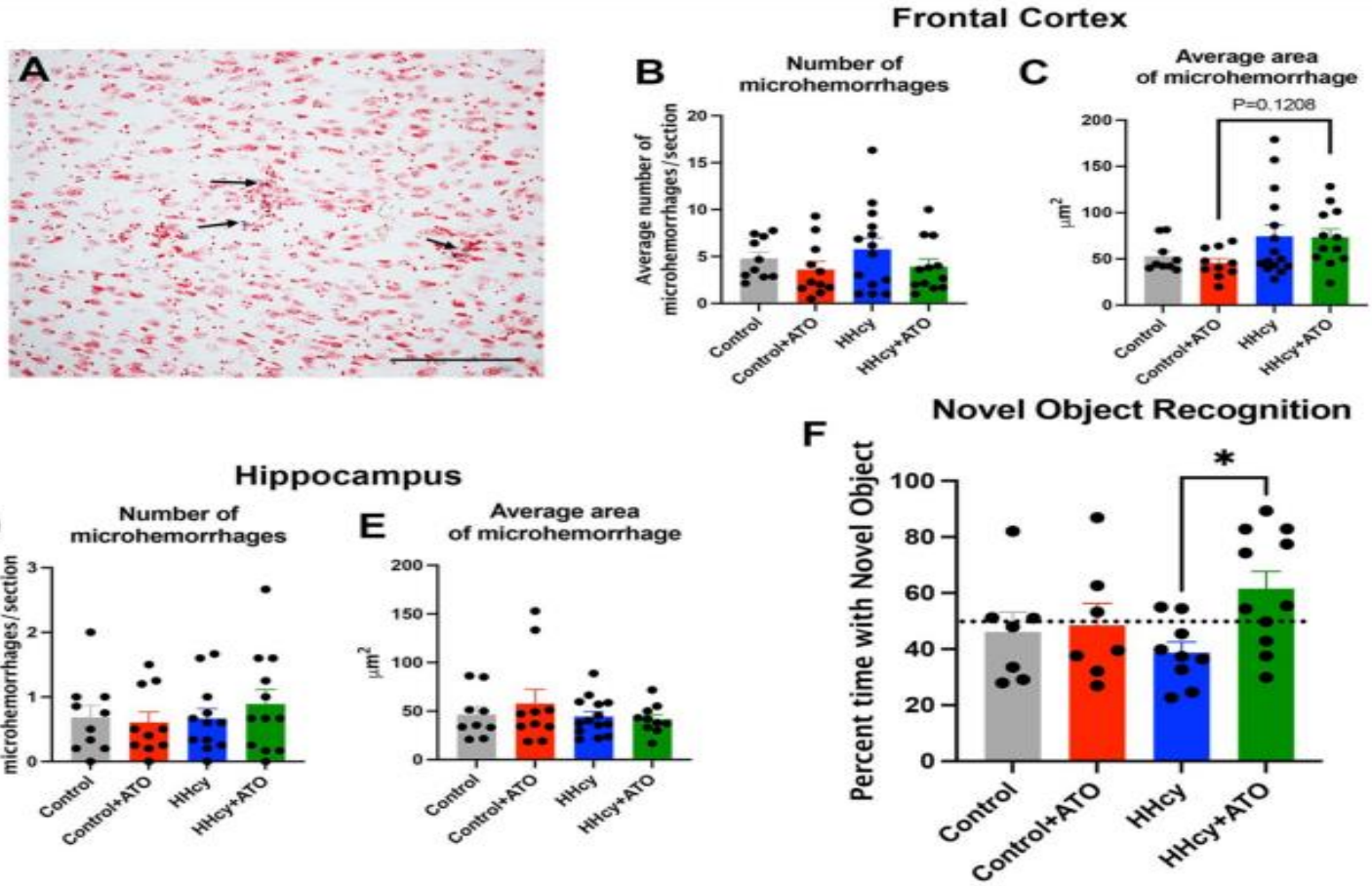
HYPOLIPIDEMICS DRUGS

SGLT2 INHIBITORS

RESEARCH Open Access

Atorvastatin rescues hyperhomocysteinemia-induced cognitive deficits and neuroinflammatory gene changes

Erica M. Weekman[1,2*], Sherika N. Johnson[1,2], Colin B. Rogers[1], Tiffany L. Sudduth[1], Kevin Xie[1], Qi Qiao[1], David W. Fardo[1], Teodoro Bottiglieri[3] and Donna M. Wilcock[1,2]



Journal of Neuroinflammation (2023) 20:199
https://doi.org/10.1186/s12974-023-02883-x

Statins and Your Memory

"Forget" About It?*

Christie M. Ballantyne, MD,[a] Vijay Nambi, MD, PhD[a,b]

Potential mechanisms of interest and concern included extremely low cholesterol level and its impact on the brain; alternatively, statin-specific effects were also considered, especially regarding water- versus lipid-soluble statins and their ability to cross the blood-brain barrier, resulting in subsequent toxicity.

Statins were not associated with incident dementia, mild cognitive impairment, or cognitive change

Effect of Statin Therapy on Cognitive Decline and Incident Dementia in Older Adults

This post hoc observational study included data from 18,446 ASPREE participants $65 years of age who had no prior CVD events, dementia, or major physical disability and were followed for a median of 4.7 years

TABLE 4 Changes in Composite Cognition and Domain-Specific Cognition Over Time Between Statin Users and Nonusers and Between Hydrophilic and Lipophilic Statin Users

	Baseline			Cognitive Change Over Time		
	β*	SE	p Value†	β‡	SE	p Value†
Statin users vs. nonusers						
3MS (global function)	−0.303	0.067	<0.001	0.006	0.021	0.79
SDMT (psychomotor speed)	0.053	0.142	0.71	0.033	0.028	0.24
COWAT (language, executive function)	−0.050	0.069	0.47	0.020	0.017	0.22
HVLT-R delayed recall (episodic memory)	−0.166	0.043	<0.001	−0.005	0.010	0.62
Composite *z* score	−0.033	0.010	0.001	0.003	0.002	0.13
Hydrophilic statins vs. lipophilic statins						
3MS (global function)	−0.095	0.118	0.42	−0.001	0.041	0.98
SDMT (psychomotor speed)	−0.159	0.248	0.52	−0.009	0.052	0.86
COWAT (language, executive function)	−0.222	0.119	0.06	−0.005	0.030	0.87
HVLT-R delayed recall (episodic memory)	−0.063	0.073	0.39	0.030	0.019	0.12
Composite *z* score	−0.024	0.018	0.18	0.000	0.003	0.97

CONCLUSIONS In adults > 65 years of age, statin therapy was not associated with incident dementia, MCI, or declines in individual cognition domains. These findings await confirmation from ongoing randomized trials. (

J Am Coll Cardiol 2021;77:3145–56)

DRUGS TO PREVENT COGNITIVE DYSFUNCTION

ANTIHYPERTENSIVE DRUGS

HYPOLIPIDEMICS DRUGS

SGLT2 INHIBITORS

Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction

Pasquale Mone,[1,2,3] Angela Lombardi,[1] Jessica Gambardella,[1,4] Antonella Pansini,[2] Gaetano Macina,[2] Maria Morgante,[2] Salvatore Frullone,[2] and Gaetano Santulli[1,4,5]

Diabetes Care 2022;45:1247–1251 | https://doi.org/10.2337/dc21-2434

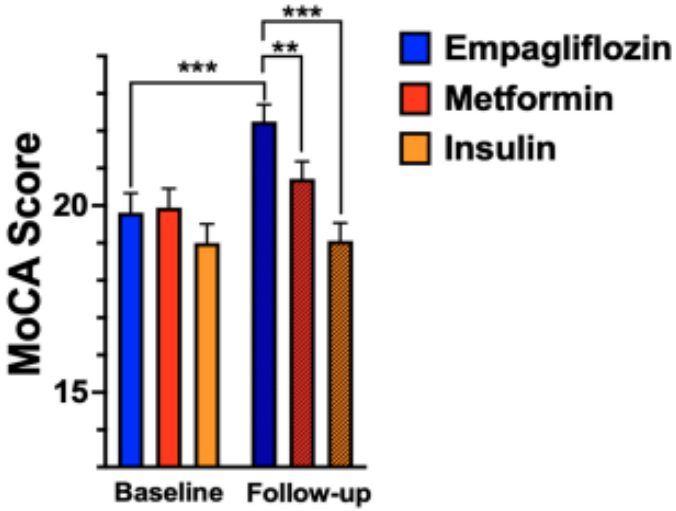


Figure 1—MoCA score in the empagliflozin, metformin, and insulin groups evaluated at baseline and follow-up. Data are means ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$.

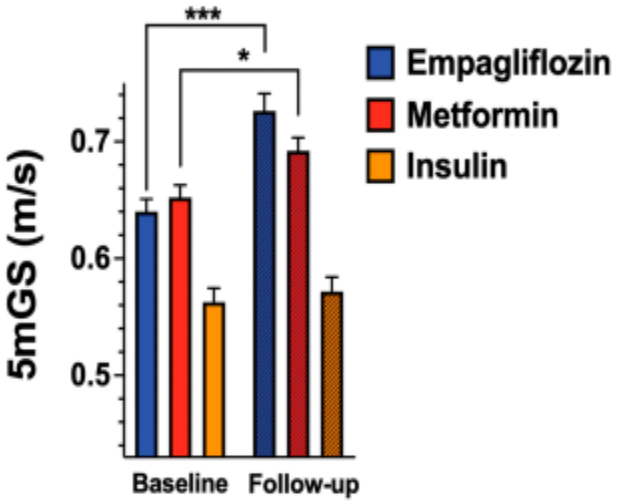


Figure 2—The 5mGS in the empagliflozin, metformin, and insulin groups measured at baseline and follow-up. Data are means ± SD. $^{*}P < 0.05$, $^{***}P < 0.001$.

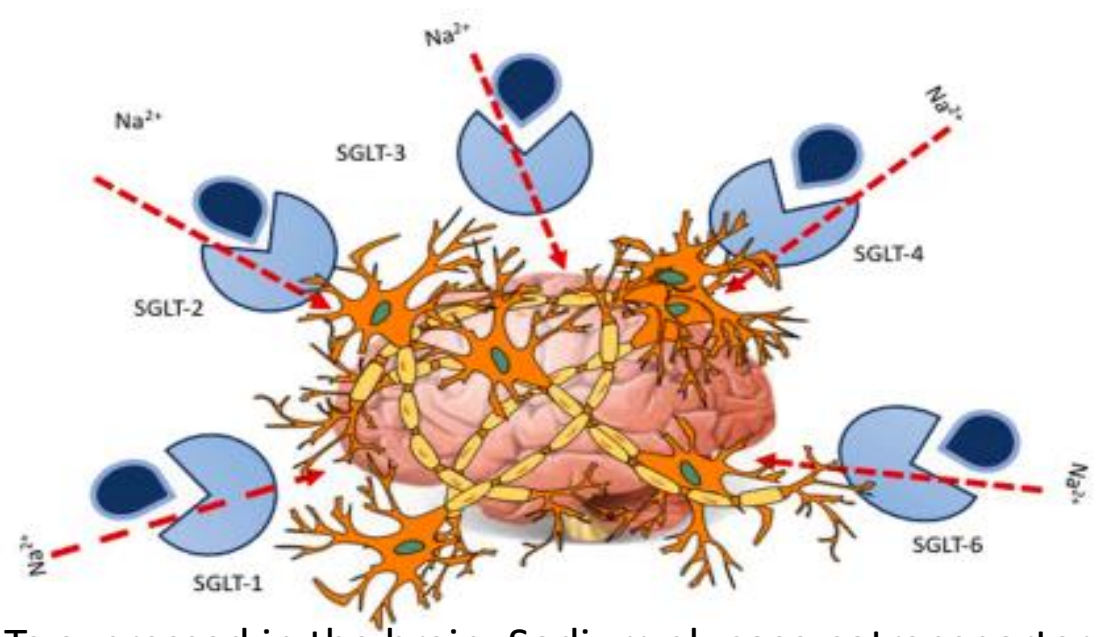
This study is the first to show significant beneficial effects of the SGLT2 inhibitor empagliflozin on cognitive and physical impairment in frail older adults with diabetes and HFpEF

Review

Cognitive impairment and type 2 diabetes mellitus: Focus of SGLT2 inhibitors treatment

Maria Rosaria Rizzo [a,*], Irene Di Meo [a], Rita Polito [a], Maria Chiara Auriemma [a], Antonio Gambardella [b], Gabriella di Mauro [c], Annalisa Capuano [c], Giuseppe Paolisso [a]

[a] Department of Advanced Medical and Surgical Sciences - University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[b] Department of Precision Medicine, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[c] Department of Experimental Medicine - Section of Pharmacology "L. Donatelli", University of Campania "Luigi Vanvitelli", 80138 Naples, Italy



The principal SGLTs expressed in the brain. Sodium glucose cotransporters (SGLTs) are fundamental in the mechanism of glucose entry into the brain cell. SGLTs transport glucose into the cell along a sodium gradient. SGLT1, SGLT2, SGLT3, SGLT4, SGLT6 have been identified in the brain. The distribution of the brainexpressed SGLTs differs strongly and, unfortunately, not all brain SGLTs have been studied extensively.

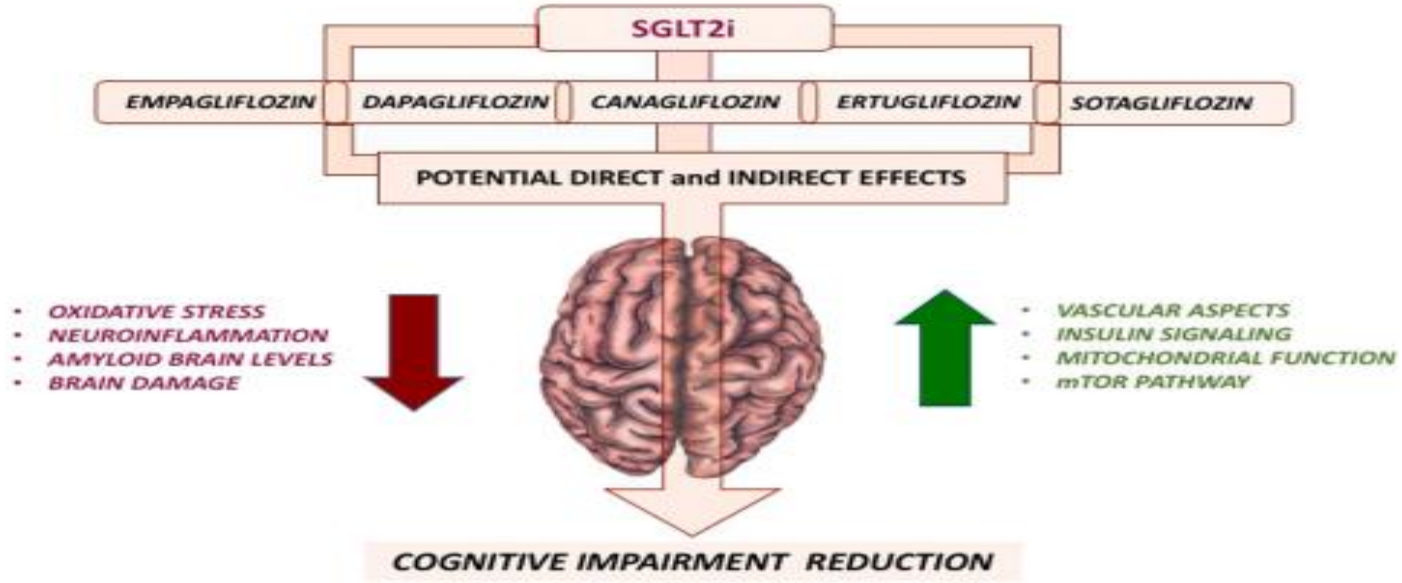
Pharmacological ResearchVolume 176, February 2022, 106062

Review

Cognitive impairment and type 2 diabetes mellitus: Focus of SGLT2 inhibitors treatment

Maria Rosaria Rizzo [a,*], Irene Di Meo [a], Rita Polito [a], Maria Chiara Auriemma [a], Antonio Gambardella [b], Gabriella di Mauro [c], Annalisa Capuano [c], Giuseppe Paolisso [a]

[a] Department of Advanced Medical and Surgical Sciences - University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[b] Department of Precision Medicine, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[c] Department of Experimental Medicine - Section of Pharmacology "L. Donatelli", University of Campania "Luigi Vanvitelli", 80138 Naples, Italy



The potential directs and indirect effects of SGLT2i on cognitive impairment

Reduction of oxidative stress, neuroinflammation, amyloid brain levels and in general brain damage, and positive impact on vascular health, insulin signaling, mitochondrial function and mTOR pathway are considered the possible underlying mechanisms.

Pharmacological ResearchVolume 176, February 2022, 106062

DRUGS TO PREVENT COGNITIVE DYSFUNCTION

ANTIHYPERTENSIVE DRUGS

HYPOLIPIDEMICS DRUGS

SGLT2 INHIBITORS

OTHER AGENTS

. 20 eb;15(2):97-109.
April 25, 2023; 100 (17) EDITORIAL

Pioglitazone and Lower Risk of Dementia

Will This Change Practice?

Colleen J. Maxwell, Wajd Alkabbani, Sevil Yasar

Lower risk of dementia with pioglitazone, compared with other second-line treatments, in metformin-based dual therapy: a population-based longitudinal study

Pioglitazone as a second-line treatment after metformin might provide a protective effect on dementia risk among individuals with type 2 diabetes.

Pioglitazone use increases risk of Alzheimer's disease in patients with type 2 diabetes receiving insulin

Thiazolidinedione use is associated with reduced risk of dementia in patients with type 2 diabetes mellitus: A retrospective cohort study

Harnessing the potential of machine learning and artificial intelligence for dementia research

Janice M. Ranson[1*], Magda Bucholc[2], Donald Lyall[3], Danielle Newby[4], Laura Winchester[4], Neil P. Oxtoby[5], Michele Veldsman[6], Timothy Rittman[7], Sarah Marzi[8,9], Nathan Skene[8,9], Ahmad Al Khleifat[10], Isabelle F. Foote[11], Vasiliki Orgeta[12], Andrey Kormilitzin[3], Ilianna Lourida[1] and David J. Llewellyn[1,13]

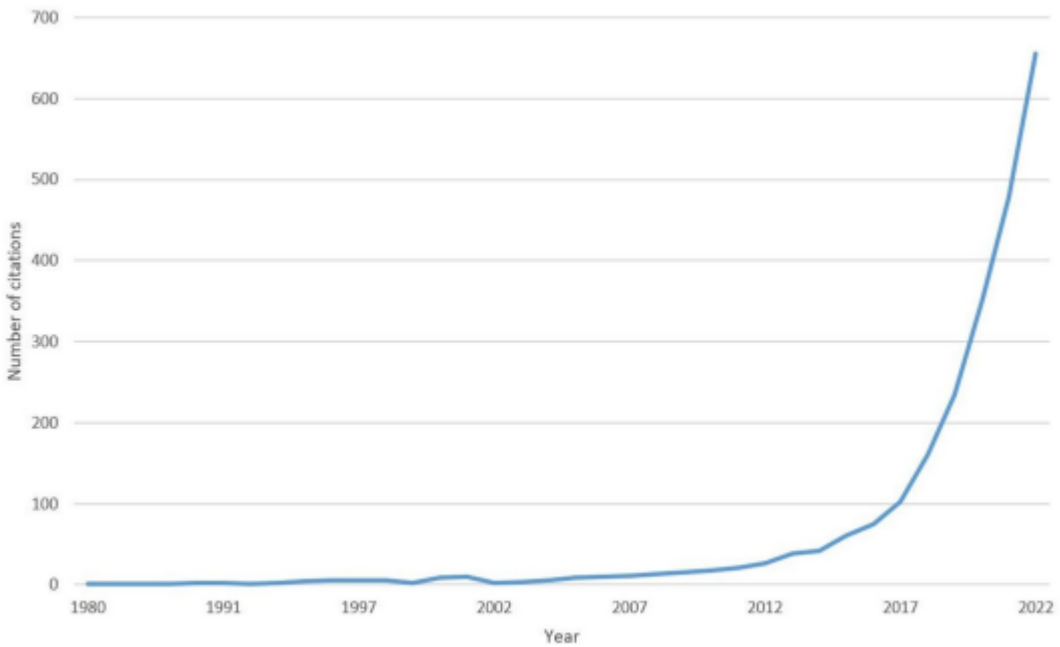


Fig. 1 Growth in citations related to AI in dementia research. Source: PubMed citations using the search term (Alzheimer*[Title/Abstract] OR dement*[Title/Abstract]) AND (AI[Title/Abstract] OR artificial intelligence[Title/Abstract] OR machine learning[Title/Abstract])

Ranson et al. Brain Informatics (2023) 1

Harnessing the potential of machine learning and artificial intelligence for dementia research

Janice M. Ranson[1*], Magda Bucholc[2], Donald Lyall[3], Danielle Newby[4], Laura Winchester[4], Neil P. Oxtoby[5], Michele Veldsman[6], Timothy Rittman[7], Sarah Marzi[8,9], Nathan Skene[8,9], Ahmad Al Khleifat[10], Isabelle F. Foote[11], Vasiliki Orgeta[12], Andrey Kormilitzin[3], Ilianna Lourida[1] and David J. Llewellyn[1,13]

Table 1 Overview of current applications, challenges and prospects for machine learning and AI applications in five key areas of dementia research

	Current areas of machine learning and AI applications	Challenges and knowledge gaps	Prospects and future directions
Genetics	Full genomic signal analysis [3, 4] Statistical fine mapping [6, 7] Single cell genomics [9, 10] Identification of causal variants [6]	Effect of specific genetic variants [5] Relation of genetic variation to cellular changes [5] Mixed evidence for interaction of genetics with modifiable risk [21–24]	Utilisation of integrative data sets [124] Combining omics data to identify functional implications [125] Application of genetic risk to individuals [15]
Experimental Medicine	Data-driven multimodal analysis [35, 36] Gene regulation [26, 27] Digital twin brain models link [33]structure, function and pathology	Translational gap from models to human disease biology [126] Lack of power in small, single modality studies [126] Poor reproducibility [127]	Efficient drug target discovery [128] Simulated ageing signatures [129] Digital brains for precision dementia research[34]
Drug discovery and Trials Optimisation	Intelligent drug target identification [16] Incorporation of multiple biomarker data [59] Natural language processing and text mining of electronic health records [68]	Heterogeneity of disease risk, severity and subtype [60, 61] Cost of longitudinal analysis [60] Restricted access to clinical trial data [64]	Enhanced identification of risk for trial recruitment [63] Utilising publicly available data and linked health records [16, 66] Multi institutional collaborative initiatives to share data [67]
Neuroimaging	Automated feature extraction for diagnosis and prediction [85] Combining imaging modalities and biomarker data [86] Investigation of disease progression and biological mechanisms [61, 87]	Lack of clinical implementation [85] Poor interpretability is challenging for regulation [91] Sensitivity to bias in the training data [91]	Validation of existing models for clinical settings [90] Availability of large data sets and repositories [85] Strategic recruitment to improve real-world applicability [91]
Prevention	Analysis of complex interactions in observational studies [113] Increased accuracy of polygenic risk and predictive models [15, 130] Validation of drug repurposing for dementia prevention [117, 118]	Inconsistent evidence for many potential risk factors [93, 95–97] Causal relationships poorly understood [98] Lack of statistical power [17]	Personalised dementia prevention interventions [122, 123] Deep learning for improved Mendelian randomisation [103, 105] Lifespan modelling to identify the optimal timing of a prevention intervention

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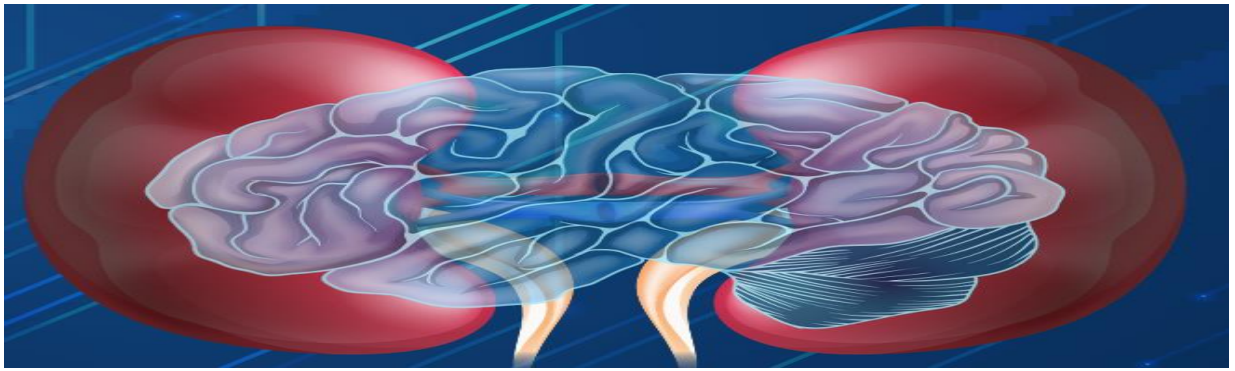

Thank You