Supplementary Online Content

Marcum ZA, Gabriel N, Bress AP, Hernandez I. Association of new use of antihypertensives that stimulate vs inhibit type 2 and 4 angiotensin II receptors with dementia among Medicare beneficiaries. *JAMA Netw Open.* 2023;6(1):e2249370. doi:10.1001/jamanetworkopen.2022.49370

- eTable 1. Antihypertensive Medications (Generic Name) by Category
- eTable 2. ICD-9 and ICD-10 Diagnosis Codes for Hypertension
- eTable 3. ICD-9 and ICD-10 Diagnosis Codes for ADRD
- **eTable 4.** Medications (Generic Names) in the Anticholinergic Cognitive Burden Score (Values of 2 or 3)
- **eTable 5.** Follow-up and Incidence Density Rates of the Secondary Outcome, by Time-Dependent Treatment Group
- **eTable 6.** Individuals in Exposure Groups by Time Period After Index Date, Among Those Remaining in the Study
- **eFigure 1.** Flowchart of Sample Selection
- **eFigure 2.** Sankey Diagram of Exposure Groups by Time Period After Index Date
- **eFigure 3.** Results of Sensitivity Analysis Multivariable Cox Proportional Hazards Model for Primary (ADRD) and Secondary (Vascular Dementia) Outcomes

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Antihypertensive Medications (Generic Name) by Category

Angiotensin II type 2 and 4	Other		
acebutolol	acetazolamide		
atenolol	aliskiren		
benazepril	ambrisentan		
bepridil	amiloride		
betaxolol	bosentan		
bisoprolol	bumetanide		
captopril	clonidine		
carteolol	deserpidine		
carvedilol	dipyridamole		
diltiazem	doxazosin		
enalapril	eplerenone		
fosinopril	ergoloid mesylates		
labetalol	ethacrynic acid		
lisinopril	ethaverine		
	furosemide		
mibefradil	guanabenz		
moexipril	guanadrel		
	guanethidine		
	guanfacine		
	hydralazine		
	isoxsuprine		
· ·	Macitentan		
•	mannitol		
	mecamylamine		
	methyldopa		
	metolazone		
	minoxidil		
	pamabrom		
	papaverine		
	papaverine		
	phenoxybenzamine		
	prazosin		
	rauwolfia serpentina		
	reserpine		
	riociguat		
	sacubitril		
	selexipag		
	spironolactone		
	terazosin		
	tolvaptan		
	torsemide		
	torsemide		
	treprostinil		
	triamterene		
	inhibiting acebutolol atenolol benazepril bepridil betaxolol bisoprolol captopril carteolol carvedilol diltiazem enalapril fosinopril labetalol lisinopril metoprolol		

eTable 2. ICD-9 and ICD-10 Diagnosis Codes for Hypertension

ICD-9	362.11, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01,
	403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13,
	404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2
ICD-10	H35.031, H35.032, H35.033, H35.039, I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2,
	I15.0, I15.1, I15.2, I15.8, I15.9, I67.4, N26.2

eTable 3. ICD-9 and ICD-10 Diagnosis Codes for ADRD

ICD-9 (any	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12,
position)	290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0,
	294.10, 294.11, 294.20, 294.21, 294.8, 797
ICD-10 (any	F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, F04, F05, F06.1, F06.8,
position)	G13.8, G30.0, G30.1, G30.8, G30.9, G31.01, G31.09, G31.1, G31.2, G94,
	R41.81, R54

Source: https://www2.ccwdata.org/web/guest/condition-categories-chronic

eTable 4. Medications (Generic Names) in the Anticholinergic Cognitive Burden Score (Values of 2 or 3)

Anticholinergc Cognitive Burden Scale
Generic name
Amitriptyline
Amoxapine
Atropine
Benztropine
Brompheniramine
Carbinoxamine
Chlorpheniramine
Chlorpromazine
Clemastine
Clomipramine
Clozapine
Darifenacin
Desipramine
Dicyclomine
Dimenhydrinate
Diphenhydramine
Doxepin
Doxylamine
Fesoterodine
Flavoxate
Hydroxyzine
Hyoscyamine
Imipramine
Meclizine
Methocarbamol
Nortriptyline
Olanzapine
Orphenadrine
Oxybutynin
Paroxetine
Perphenazine
Promethazine
Propantheline
Propiverine
Quetiapine
Scopolamine
Solifenacin
Thioridazine
Tolterodine
Trifluoperazine
Trihexyphenidyl

Trimipramine
Trospium
Amantadine
Belladonna Multiple
Carbamazepine
Cyclobenzaprine
Cyproheptadine
Loxapine
Meperidine
Methotrimeprazine
Molindone
Nefopam
Oxcarbazepine
Pimozide

eTable 5. Follow-up and Incidence Density Rates of the Secondary Outcome, by Time-Dependent Treatment Group^a

Follow-up	AT2R/AT4R Stimulating	AT2R/AT4R Inhibiting	Mixed	Non-Users
At year 3	-	-	-	-
Patient-years	20478	36760	13245	98452
No. patients newly diagnosed	14	55	14	86
with vascular dementia	0.07.(0.04	0.45 (0.40	0.44 (0.00	0.00 (0.07
Cumulative incidence	0.07 (0.04-	0.15 (0.12-	0.11 (0.06-	0.09 (0.07-
per 100 person- years (95% CI)	0.12)	0.20)	0.18)	0.11)
At year 6	-	-	-	-
Patient-years	44159	75285	30110	158359
No. patients newly diagnosed with vascular dementia	79	221	73	368
Cumulative incidence	0.18 (0.14-	0.29 (0.26-	0.24 (0.19-	0.23 (0.21-
per 100 person- years (95% CI)	0.22)	0.34)	0.31)	0.26)
At year 9	-	-	-	-
Patient-years	60647	101661	43199	188808
No. patients newly diagnosed with vascular dementia	146	406	153	602
Cumulative incidence	0.24 (0.21-	0.40 (0.36-	0.35 (0.30-	0.32 (0.29-
per 100 person- years (95% CI)	0.28)	0.44)	0.42)	0.35)
At study end	-	-	-	-
Patient-years	66796	111155	48603	198640
No. patients newly diagnosed	187	513	179	725
with vascular dementia				
Cumulative incidence	0.28 (0.24-	0.46 (0.42-	0.37 (0.32-	0.37 (0.34-
per 100 person- years (95% CI)	0.32)	0.50)	0.43)	0.39)

Abbreviations: AT2R, angiotensin II receptor type 2; AT4R, angiotensin II receptor type 4; CI, confidence interval

^aTreatment group was defined in a time dependent fashion, at each 30-day interval. Angiotensin II receptor type 2 and 4-stimulating antihypertensives defined as use of angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and/or thiazides. Angiotensin II receptor type 2 and 4-inhibiting antihypertensives defined as use of angiotensin-converting enzyme inhibitors, ß-blockers, and/or non-dihydropyridine calcium channel blockers. Mixed antihypertensive users defined as both angiotensin II receptor type 2 and 4-stimulating and -inhibiting antihypertensives.

eTable 6. Individuals in Exposure Groups by Time Period After Index Date, Among Those Remaining in the Study

	Year 0	Year 3	Year 6	Year 9
Stimulating, n (% of total)	4,879 (8.4%)	7,917 (15.4%)	6,434 (18.5%)	3,377 (20.1%)
Inhibiting, n (% of total)	10,302 (17.8%)	12,981 (25.3%)	10,220 (29.4%)	5,248 (31.2%)
Mixed, n (% of total)	2,179 (3.8%)	5,382 (10.5%)	4,861 (14.0%)	2,795 (16.6%)
None, n (% of total)	40,413 (70.0%)	24,977 (48.7%)	13,268 (38.1%)	5,407 (32.1%)
Total, n	57,773	51,257	34,783	16,827

Included people with a claim for hypertension in 2007-2014. Earliest claim date becomes index date N = 2,2612,287

•

Constrain to people who were continuously enrolled in Medicare fee-for-service (Parts A + B + stand alone prescription drug plan) for at least 12 months before index date

N = 653,534

•

Exclude people with claim for hypertension in 12 months prior to index date

N = 367,331

1

Constrain to people who filled a prescription for an antihypertensive after index date

N = 292,839

*

Exclude people who filled a prescription for an antihypertensive in 12 months prior to index date

N = 121,928

•

Exclude people with claim for Alzheimer's Disease and Related Dementias (ADRD) (primary) or vascular dementia (secondary) before filling prescription for antihypertensive

N = 106,469

•

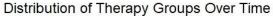
Exclude people who died, disenrolled, or had claim for ADRD or vascular dementia within 360 days of index date

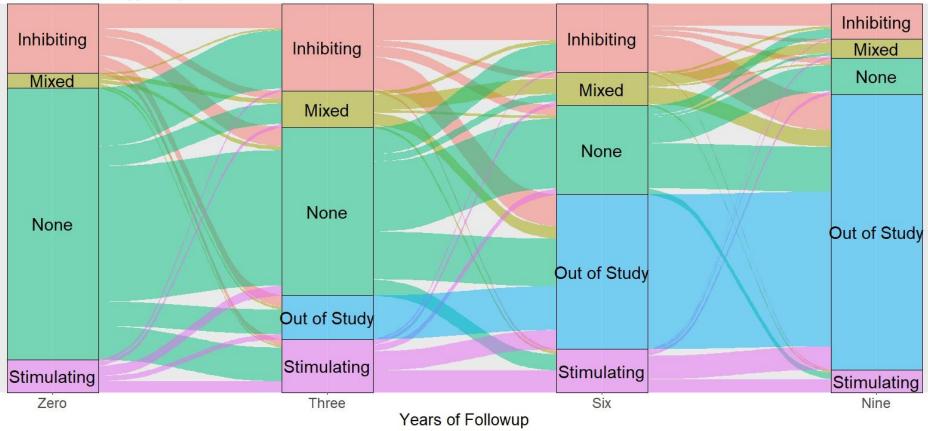
N = 84,041

Exclude people with age < 65 at index date

N = 57,773

eFigure 2. Sankey Diagram of Exposure Groups by Time Period After Index Date





This figure shows transitions across time-dependent treatment groups over the study follow-up. Angiotensin II receptor type 2 and 4-stimulating antihypertensives defined as use of angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and/or thiazides. Angiotensin II receptor type 2 and 4-inhibiting antihypertensives defined as use of angiotensin-converting enzyme inhibitors, \(\mathcal{B}\)-blockers, and/or non-dihydropyridine calcium channel blockers. Mixed antihypertensive users defined as both angiotensin II receptor type 2 and 4-stimulating and -inhibiting antihypertensives. "Out of Study" is defined as an individual being censored.

eFigure 3. Results of Sensitivity Analysis - Multivariable Cox Proportional Hazards Model for Primary (ADRD) and Secondary (Vascular Dementia) Outcomes

Variable	P-value	Hazard Ratio of ADRD (95%	CI)		P-value	Hazard Ratio of Vascul	ar Dementia (95	% CI)	
Stimulating vs. Inhibiting Treatment	<0.001	0.83 (95% CI 0.78, 0.88)	H ● H		0.004	0.79 (95% CI 0.67, 0.93)	⊢		
Mixed vs. Inhibiting Treatment	0.029	0.94 (95% CI 0.88, 0.99)	H●		0.102	0.88 (95% CI 0.76, 1.02)	_	 H	
No Treatment vs. Inhibiting Treatment	<0.001	0.91 (95% CI 0.87, 0.96)	Ю		0.726	1.02 (95% CI 0.91, 1.15)	· -	← ⊣	
Age, per 1 year increase	<0.001	1.10 (95% CI 1.09, 1.10)		•	<0.001	1.07 (95% CI 1.06, 1.08)		•	
Female vs Male	<0.001	0.92 (95% CI 0.88, 0.96)	H		0.090	0.91 (95% CI 0.81, 1.01)	⊢●-		
Black vs Non-Hispanic White	<0.001	1.38 (95% CI 1.27, 1.50)		⊢• ⊣	<0.001	1.59 (95% CI 1.30, 1.95)		⊢	
Hispanic vs Non-Hispanic White	0.123	0.91 (95% CI 0.80, 1.03)	⊢•	ł	0.178	0.80 (95% CI 0.57, 1.11)	⊢	H	
Other Race/ethnicity vs Non-Hispanic White	0.005	0.87 (95% CI 0.79, 0.96)	 -		0.009	0.70 (95% CI 0.53, 0.91)	──		
Low-Income Subsidy	<0.001	1.50 (95% CI 1.44, 1.57)		I⊕I	<0.001	1.48 (95% CI 1.32, 1.66)		⊢	
Atrial Fibrillation	<0.001	1.11 (95% CI 1.06, 1.17)		I ⊕I	0.007	1.18 (95% CI 1.05, 1.33)		⊢	
Congestive Heart Failure	< 0.001	1.39 (95% CI 1.33, 1.46)		l ⊕ l	< 0.001	1.36 (95% CI 1.21, 1.52)		⊢	
Chronic Kidney Disease	< 0.001	1.37 (95% CI 1.31, 1.43)		₩	< 0.001	1.49 (95% CI 1.34, 1.66)		⊢●⊣	
Depression	< 0.001	1.88 (95% CI 1.80, 1.96)		₩	< 0.001	2.54 (95% CI 2.28, 2.82)			⊢
Diabetes	< 0.001	1.10 (95% CI 1.05, 1.14)		Hel	0.029	1.12 (95% CI 1.01, 1.25)	l	→ -I	
Ischemic Heart Disease	< 0.001	1.12 (95% CI 1.07, 1.17)		Hel	0.918	1.01 (95% CI 0.90, 1.13)	\vdash	H	
Stroke	<0.001	1.71 (95% CI 1.63, 1.78)		l o l	<0.001	3.21 (95% CI 2.90, 3.56)			⊢●
Anticholingeric Use	<0.001	1.13 (95% CI 1.08, 1.19)		н о н	0.220	0.93 (95% CI 0.82, 1.05)	⊢•	-	
NSAID Use	0.597	0.99 (95% CI 0.94, 1.04)	н	н	0.403	0.95 (95% CI 0.83, 1.08)	⊢ •	Ħ	
Statin use	< 0.001	0.89 (95% CI 0.85, 0.93)	₩		0.022	0.87 (95% CI 0.78, 0.98)	⊢•-		
Use of Other Antihypertensive Drugs	0.043	0.95 (95% CI 0.91, 1.00)	I⊕		< 0.001	0.75 (95% CI 0.65, 0.86)	⊢●─		
		0.5		1 2			0.5	2	4
		D	ecreases	Increases			Decreases	Increases	
		4_	ADRD	ADRD		Vas	scular Dementia		nentia
ALL COMPONENTS OF			. .						

Abbreviations: ADRD, Alzheimer's disease and related dementias; CI, confidence interval

This figure displays two separate multivariable Cox proportional hazards models for primary (ADRD) and secondary (vascular dementia) outcomes.

The stimulating group was defined as having at least 1 day of the 30-day interval with possession of stimulating antihypertensive medication and 0 days with possession of inhibiting medication. The inhibiting group was defined as having at least 1 day of the 30-day interval with possession of inhibiting antihypertensive medication and 0 days with possession of stimulating medication. The mixed group was defined as having at least 1 day of the 30-day interval with possession of inhibiting antihypertensive medication and at least 1 day with possession of stimulating antihypertensive medication. The non-users group was defined as having 0 days with possession of inhibiting antihypertensive medication.

Angiotensin II receptor type 2 and 4-stimulating antihypertensives defined as use of angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and/or thiazides. Angiotensin II receptor type 2 and 4-inhibiting antihypertensives defined as use of angiotensin-converting enzyme inhibitors, \(\mathbb{G}\)-blockers, and/or non-dihydropyridine calcium channel blockers. Mixed antihypertensive users defined as both angiotensin II receptor type 2 and 4-stimulating and -inhibiting antihypertensives.