

Supplementary Online Content

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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 stimulating	Angiotensin II type 2 and 4 inhibiting	Other
amlodipine azilsartan bendroflumethiazide candesartan chlorothiazide chlorthalidone eprosartan felodipine hydrochlorothiazide hydroflumethiazide indapamide irbesartan isradipine losartan methyclothiazide nicardipine nifedipine nimodipine nisoldipine olmesartan polythiazide telmisartan trichlormethiazide valsartan	acebutolol atenolol benazepril bepridil betaxolol bisoprolol captopril carteolol carvedilol diltiazem enalapril fosinopril labetalol lisinopril metoprolol mibefradil moexipril nadolol nebivolol penbutolol perindopril pindolol propranolol quinapril ramipril sotalol timolol trandolapril verapamil verapamil	acetazolamide aliskiren ambrisentan amiloride bosentan bumetanide clonidine deserpidine dipyridamole doxazosin eplerenone ergoloid mesylates ethacrynic acid ethaverine furosemide guanabenz guanadrel guanethidine guanfacine hydralazine isoxsuprine Macitentan mannitol mecamylamine methyl dopa metolazone minoxidil pamabrom papaverine papaverine phenoxybenzamine prazosin rauwolfia serpentina reserpine riociguat sacubitril selexipag spironolactone terazosin tolvaptan torsemide torsemide treprostinil triamterene

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 position)	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 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 position)	F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, F04, F05, F06.1, F06.8, 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)

Anticholinergic 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
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Propiverine
Quetiapine
Scopolamine
Solifenacin
Thioridazine
Tolterodine
Trifluoperazine
Trihexyphenidyl

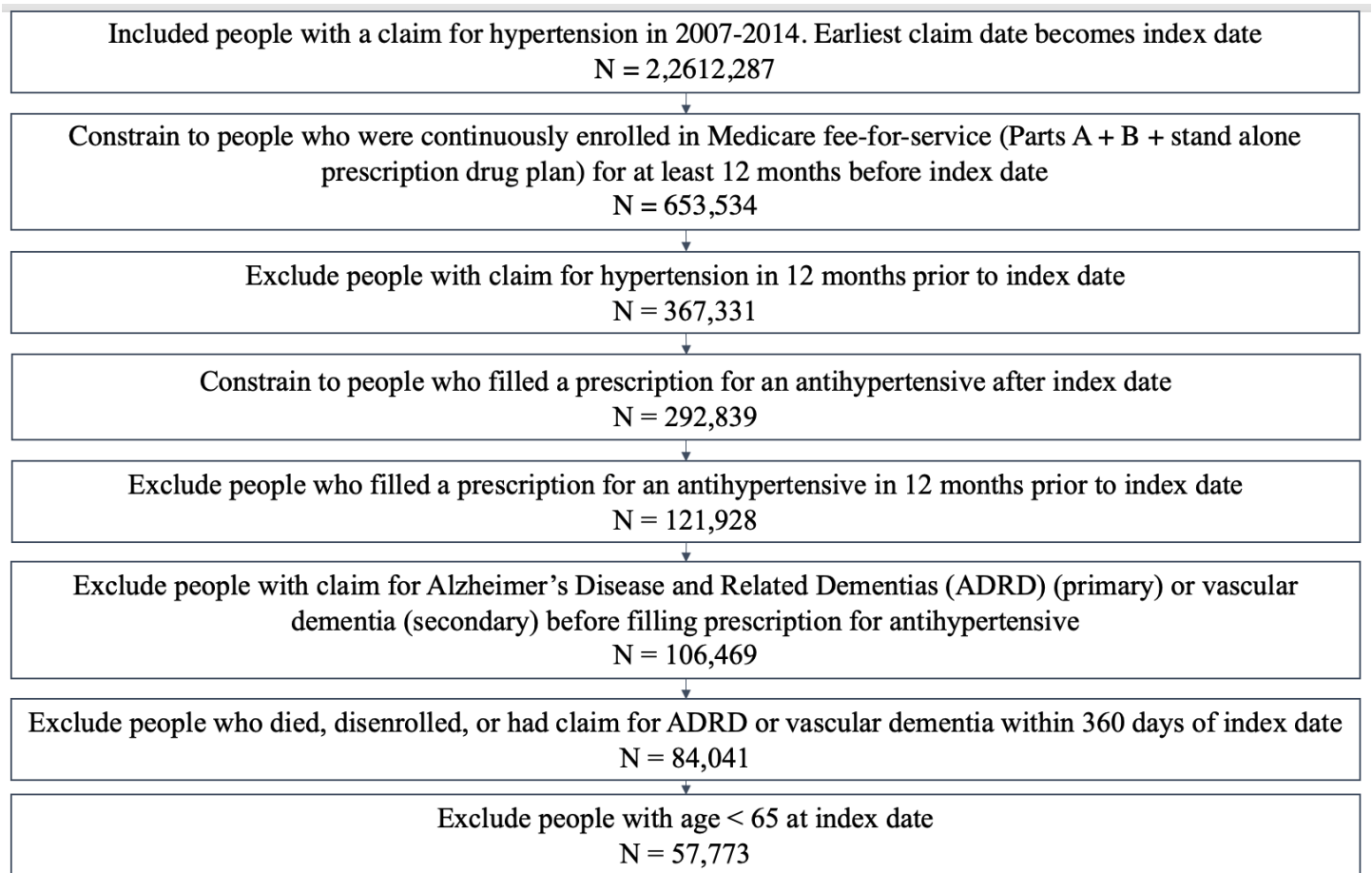
Trimipramine
Trospium
Amantadine
Belladonna Multiple
Carbamazepine
Cyclobenzaprine
Cyproheptadine
Loxapine
Meperidine
Methotrimeprazine
Molindone
Nefopam
Oxcarbazepine
Pimozide

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 with vascular dementia	14	55	14	86
Cumulative incidence per 100 person- years (95% CI)	0.07 (0.04-0.12)	0.15 (0.12-0.20)	0.11 (0.06-0.18)	0.09 (0.07-0.11)
At year 6	-	-	-	-
Patient-years	44159	75285	30110	158359
No. patients newly diagnosed with vascular dementia	79	221	73	368
Cumulative incidence per 100 person- years (95% CI)	0.18 (0.14-0.22)	0.29 (0.26-0.34)	0.24 (0.19-0.31)	0.23 (0.21-0.26)
At year 9	-	-	-	-
Patient-years	60647	101661	43199	188808
No. patients newly diagnosed with vascular dementia	146	406	153	602
Cumulative incidence per 100 person- years (95% CI)	0.24 (0.21-0.28)	0.40 (0.36-0.44)	0.35 (0.30-0.42)	0.32 (0.29-0.35)
At study end	-	-	-	-
Patient-years	66796	111155	48603	198640
No. patients newly diagnosed with vascular dementia	187	513	179	725
Cumulative incidence per 100 person- years (95% CI)	0.28 (0.24-0.32)	0.46 (0.42-0.50)	0.37 (0.32-0.43)	0.37 (0.34-0.39)
Abbreviations: AT2R, angiotensin II receptor type 2; AT4R, angiotensin II receptor type 4; CI, confidence interval				
^a Treatment 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, β-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

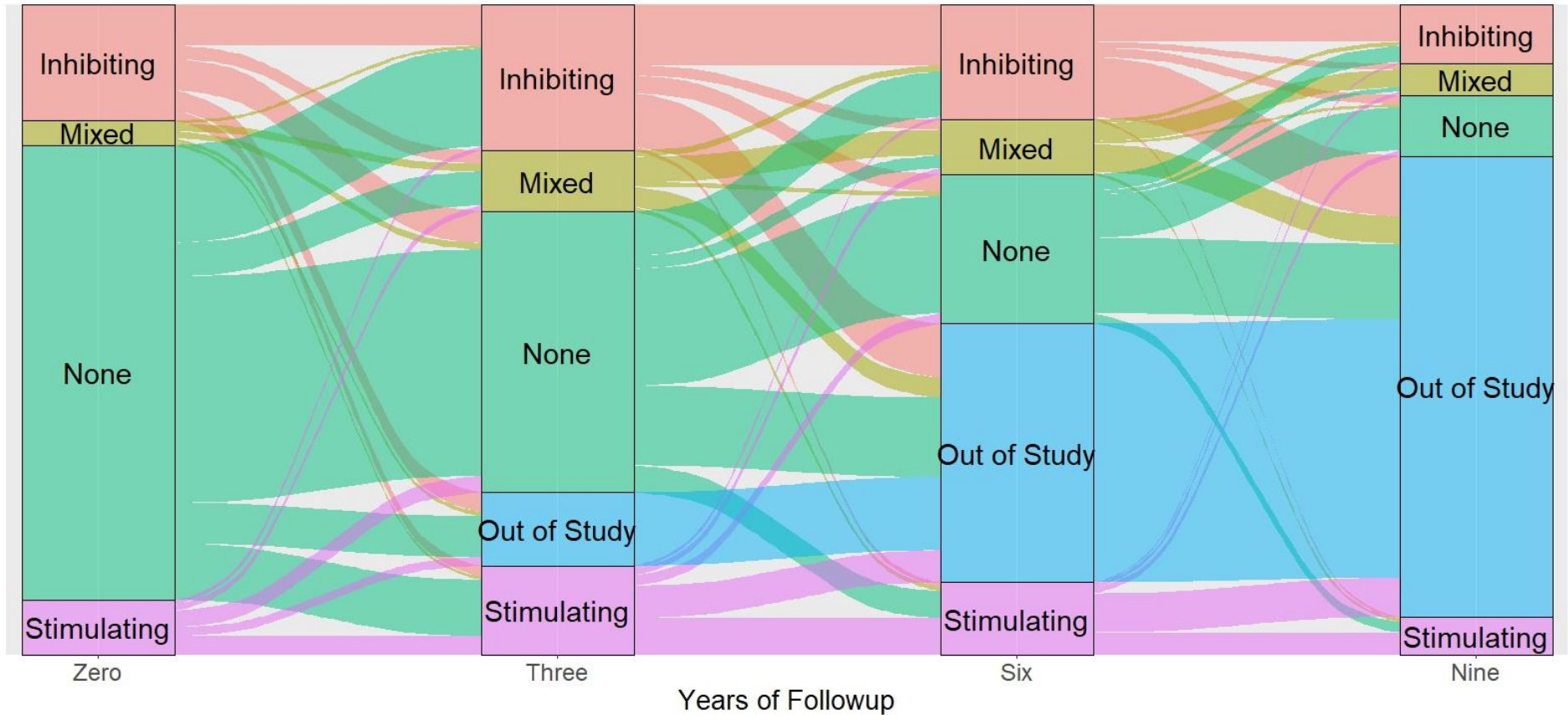
	Year 0	Year 3	Year 6	Year 9
Stimulating, n (% of total)	4,879 (8.4%)	7,917 (15.4%)	6,434 (18.5%)	3,377 (20.1%)
Inhibiting, n (% of total)	10,302 (17.8%)	12,981 (25.3%)	10,220 (29.4%)	5,248 (31.2%)
Mixed, n (% of total)	2,179 (3.8%)	5,382 (10.5%)	4,861 (14.0%)	2,795 (16.6%)
None, n (% of total)	40,413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

eFigure 1. Flowchart of Sample Selection



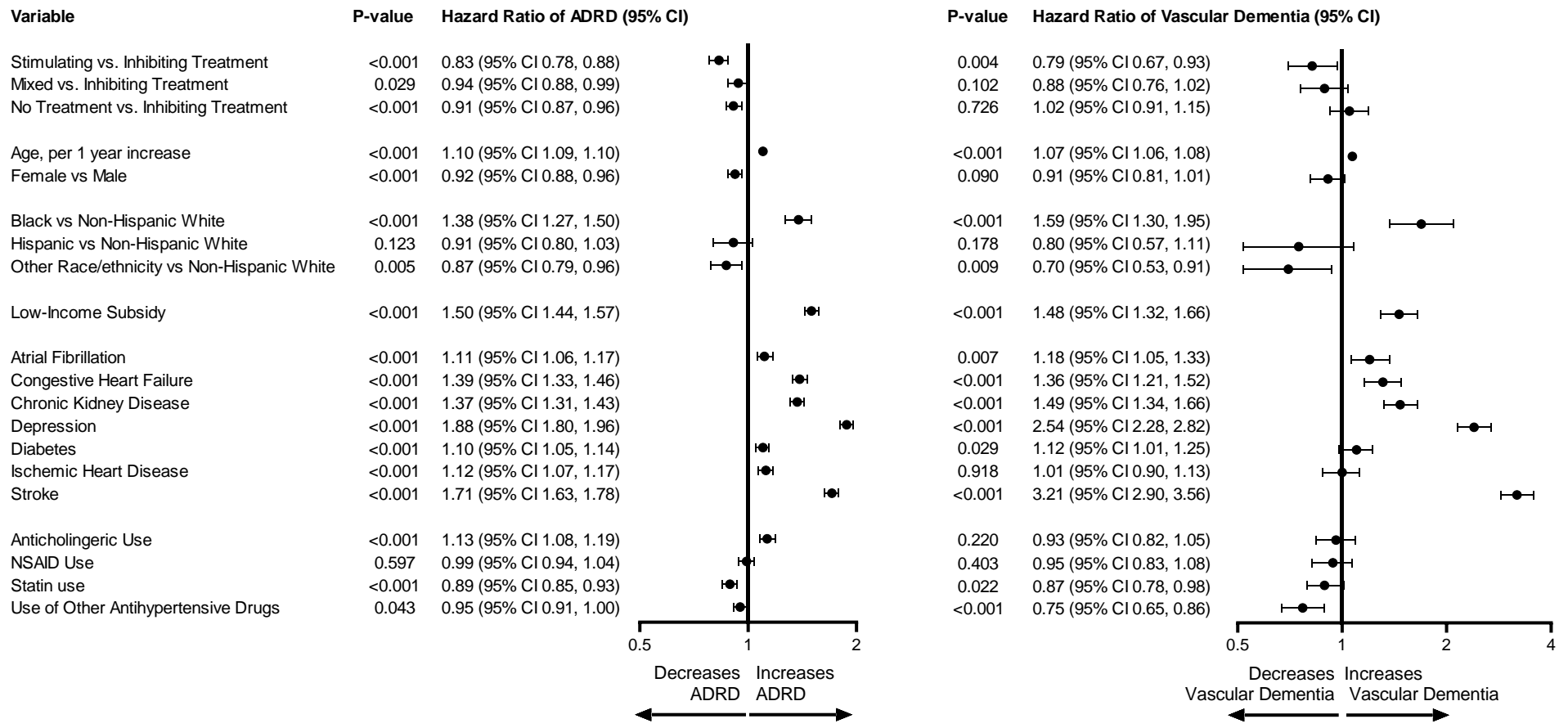
eFigure 2. Sankey Diagram of Exposure Groups by Time Period After Index Date

Distribution of Therapy Groups Over Time



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, β -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



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 and 0 days with possession of stimulating 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, β-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.