## Title
Association of Antihypertensives and Cognitive Impairment in Long-Term Care Residents.



## Journal
Journal of Alzheimer's Disease, 86(3)

## ISSN
1387-2877

## Authors
Marcum, Zachary A
Li, Yongmei
Lee, Sei J
et al.

## Publication Date
2022

## DOI
10.3233/jad-215393

Peer reviewed

HHS Public Access

Author manuscript

*J Alzheimers Dis*. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

*J Alzheimers Dis*. 2022 ; 86(3): 1149–1158. doi:10.3233/JAD-215393.

# Association of Antihypertensives and Cognitive Impairment in Long-term Care Residents

**Zachary A. Marcum, PharmD, PhD**[a], **Yongmei Li, PhD**[b], **Sei J. Lee, MD, MAS**[c,d], **Michael A. Steinman, MD**[c,d], **Laura Graham, PhD, MPH**[e,f], **Bocheng Jing, MS**[g], **Kathy Fung, MS**[c,d], **Carmen A. Peralta, MD**[h], **Michelle C. Odden, PhD**[b,i]

[a]Department of Pharmacy, University of Washington, Seattle, WA, USA

[b]Department of Epidemiology and Population Health, Stanford University, Stanford, CA, USA

[c]San Francisco VA Medical Center, San Francisco, CA, USA

[d]Department of Medicine, University of California San Francisco, San Francisco, CA, USA

[e]Department of Surgery, Stanford University, Stanford, CA, USA

[f]Health Economics Research Center, VA Palo Alto Health Care System, Palo Alto, CA, USA

[g]NCIRE – The Veterans Health Research Institute, San Francisco. USA

[h]Cricket Health, Inc and the Kidney Health Research Collaborative, University of California San Francisco and San Francisco VA Medical Center, San Francisco, CA, USA

[i]Geriatric Research Education and Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA, USA

## Abstract

**Background:** Certain classes of antihypertensive medication may have different associations with cognitive impairment.

**Corresponding author**: Zachary A. Marcum, PharmD, PhD, Department of Pharmacy, School of Pharmacy, University of Washington, 1959 NE Pacific St, Box 357630, Seattle, WA 98102 (zmarcum@uw.edu), Phone 206-685-2559, Fax 206-543-3835, @zacharyamarcum.

AUTHORSHIP

- *Study concept and design*: Marcum, Li, Lee, Steinman, Odden
- *Acquisition of data*: Li, Graham, Jing, Fung, Odden
- *Analysis and interpretation of data*: Marcum, Li, Lee, Steinman, Graham, Jing, Fung, Peralta, Odden
- *Drafting of the manuscript*: Marcum, Li, Odden
- *Critical revision of the manuscript for important intellectual content*: Marcum, Li, Lee, Steinman, Graham, Jing, Fung, Peralta, Odden
- *Final approval of the version to be published*: Marcum, Li, Lee, Steinman, Graham, Jing, Fung, Peralta, Odden
- *Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved*: Marcum, Li, Lee, Steinman, Graham, Jing, Fung, Peralta, Odden

CONFLICTS OF INTEREST/DISCLOSURE STATEMENT

The authors have no conflict of interest to report.

**Objective:** To examine the association between prevalent use of antihypertensive medications that stimulate (thiazides, dihydropyridine calcium channel blockers, angiotensin type I receptor blockers) vs. inhibit (angiotensin-converting enzyme inhibitors, beta-blockers, non-dihydropyridine calcium channel blockers) type 2 and 4 angiotensin II receptors on cognitive impairment among older adults residing in Veterans Affairs (VA) nursing homes for long-term care.

**Methods:** Retrospective cohort study. Long-term care residents aged 65+ years admitted to a VA nursing home from 2012 to 2019 using blood pressure medication and without cognitive impairment at admission. Main exposure was prevalent use of angiotensin II receptor type 2 and 4-'stimulating' (N=589), 'inhibiting' (N=3219), or 'mixed' (N=1715) antihypertensive medication regimens at admission. Primary outcome was any cognitive impairment (Cognitive Function Scale).

**Results:** Over an average of 5.4 months of follow-up, prevalent use of regimens containing exclusively 'stimulating' antihypertensives was associated with a lower risk of any incident cognitive impairment as compared to prevalent use of regimens containing exclusively 'inhibiting' antihypertensives (HR 0.83, 95% CI 0.74-0.93). Results for the comparison between 'mixed' vs. 'inhibiting' regimens were in the same direction but not statistically significant (HR 0.96, 95% CI 0.88-1.06).

**Conclusion:** For residents without cognitive impairment at baseline, prevalent users of regimens containing exclusively antihypertensives that stimulate type 2 and 4 angiotensin II receptors had lower rates of cognitive impairment as compared to prevalent users of regimens containing exclusively antihypertensives that inhibit these receptors. Residual confounding cannot be ruled out.

### Keywords

antihypertensives; antihypertensive drugs; aged; cognitive dysfunction

## INTRODUCTION

Lower blood pressure (BP), especially in mid-life, is associated with lower risk of dementia [1,2], and recent trial data have shown that more intensive systolic BP control reduces mild cognitive impairment (MCI) and dementia risk even at older ages [3]. Certain classes of antihypertensive medication may have different associations with cognitive impairment. Animal and mechanistic data show that antihypertensive medications that stimulate type 2 and 4 angiotensin II receptors promote beneficial effects on the brain, possibly through reduced ischemia, enhanced cerebral blood flow, and improved spatial memory processing, among other pathways [4-11]. Data from one observational study suggest that angiotensin II receptor type 2 and 4-stimulating antihypertensives (angiotensin II receptor type 1 antagonists (ARBs), dihydropyridine calcium channel blockers [CCBs], and thiazides) are associated with lower risk of dementia compared to angiotensin II receptor type 2 and 4-inhibiting antihypertensives (angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and non-dihydropyridine calcium channel blockers), independent of blood pressure [12]. However, these findings need to be replicated in independent samples. Moreover,

little is known about the association between antihypertensive use and cognitive outcomes in nursing home residents [13] – a population with a high prevalence of multimorbidity, polypharmacy, frailty, and increased risk of poor cognitive outcomes.

In this study, we examined the association between prevalent use of antihypertensive medications that stimulate versus inhibit type 2 and 4 angiotensin II receptors on cognitive impairment among older adults residing in VA nursing homes for long-term care. This study was conducted in a cohort of Veterans on BP-lowering treatment and residing in long-term care in the period 2012 to 2019 [14].

## MATERIALS AND METHODS

### Study Population

We constructed a retrospective cohort of residents in VA nursing homes, which are known as Community Living Centers (CLCs). Residents were initially excluded if they (1) had a CLC stay <90 days to exclude those undergoing post-acute rehabilitation; (2) were <65 years at admission; (3) had a >30-day acute hospital stay during their CLC stay; and (4) had no BP measures. For this analysis, residents ≥ 65 years of age with long-term stays and BP measured during their NH stay were included if they were admitted to a CLC ward between July 1, 2012 (date of first Cognitive Function Score [CFS] measure via Minimum Data Set [MDS] 3.0 [15]) and September 30, 2019 (N = 23,031). Residents were further excluded from the analytic cohort if they: (1) were not administered at least one antihypertensive of interest (i.e., ARBs, dihydropyridine calcium channel blockers, thiazides, ACE-inhibitors, beta-blockers, and non-dihydropyridine calcium channel blockers) in the first week after admission; (2) had a dementia diagnosis at NH admission; (3) did not have a CFS measure via MDS 3.0 [15] during the NH stay; (4) had any cognitive impairment (CFS = 2 or 3 or 4) at NH admission. This resulted in a final analytic sample of 5,047 residents (Figure 1). Follow-up was censored at discharge, death, entry into hospice, or on June 1, 2020. This study received institutional review board approval with a waiver of informed consent from Stanford University and the VA Palo Alto Health Care System.

### Measures

The VA supports a network-wide national electronic health record with a master patient index that links all patients receiving care at all VA facilities. The primary data source for this study was the VA Corporate Data Warehouse (CDW), and CLC stays were identified using validated methods. We linked data from resident assessments in the MDS, which is a federally mandated clinical assessment of all residents in Medicare or Medicaid certified nursing homes. This assessment includes a standardized evaluation of residents' cognitive status, the CFS [15].

Data on antihypertensive medication use were captured from the Bar-Coded Medication Administration (BCMA) data, which provide a granular assessment of each medication administered at a VA facility. Antihypertensive medications were identified by VA Drug Classification Code and reviewed to ensure that the primary indication was BP-lowering (e.g., did not include sildenafil). Furthermore, residents were classified into 1 of 3 mutually

exclusive antihypertensive regimen exposure categories at NH admission (prevalent use, in the first week): (1) use of only angiotensin II receptor type 2 and 4-'stimulating' antihypertensives (ARBs, dihydropyridine calcium channel blockers, and thiazides); (2) use of only angiotensin II receptor type 2 and 4-'inhibiting' antihypertensives (ACE-inhibitors, beta-blockers, and non-dihydropyridine calcium channel blockers); or (3) use of at least one antihypertensive medication from both (1) and (2) (i.e., 'mixed' regimens). Use of other antihypertensives (loop diuretics, central alpha-blockers, vasodilators, and potassium-sparing diuretics) were classified as "other" antihypertensive use and used for adjustment.

The primary outcome was first occurrence of any cognitive impairment. Data on cognitive function were obtained from the MDS 3.0. We used the CFS as a single, integrated, 4-level assessment of cognitive function: cognitively intact (CFS=1), mildly impaired (CFS=2), moderately impaired (CFS=3), and severely impaired (CFS=4). The outcome of any cognitive impairment was defined as time to first occurrence of any mild, moderate, or severe cognitive impairment.

The CDW Patient domain was used to determine patient age, sex, race, and ethnicity. Data on BP levels and weight were pulled from the CDW Vital Signs domain. Chronic conditions were identified using ICD-9-CM and ICD-10-CM diagnosis codes one year prior to and during the nursing home stay. Diagnosis codes were obtained from the CDW Inpatient and Outpatient domains. Death was measured from the CDW vital status domain and restricted for analysis to death occurring during the NH stay.

## Statistical Analysis

We first described the characteristics of the analytic sample upon admission, by antihypertensive use category. We conducted Cox regression analyses using age (at NH admission) as the time scale. We used age as the time scale since age is a strong predictor of cognitive function and, in doing so, effectively match for age. Any cognitive impairment was the primary outcome and antihypertensive category (all 3 categories together in one model with the 'inhibiting' group as the reference) was the independent variable. In longitudinal analyses of NH residents, competing risk of death is a major potential source of bias. To assess this, we used cause-specific hazard models for the outcome of any cognitive impairment and removed individuals who died from the risk set at the date of their death. Variables included in the adjusted model were selected *a priori* based on previous literature [1]. The adjusted model included sex, race, fiscal year of NH admission, NH district, use of other antihypertensives, total number of antihypertensives, systolic BP (first week average), diastolic BP (first week average), diabetes, atrial fibrillation, heart failure, coronary heart disease, cerebral vascular disease, BMI, and renal failure (diagnosis codes listed in Supplementary Table 1). The proportional hazards assumption for the Cox regression was tested using a statistical test based on Schoenfeld residuals. Robustness of the longitudinal primary analysis was assessed in two ways: (1) using multinomial logistic regression to generate predicted probabilities of receiving each of the three exposure categories, generating inverse probability treatment weight (IPTW) variables, and then estimating hazard ratios (HRs) using IPTW-weighted Cox regression, and (2) with a cross-sectional analysis. Given the high prevalence of cognitive impairment at NH

admission that resulted in a sizable proportion of residents being excluded in the primary analysis, a sensitivity analysis retained residents with cognitive impairment (per the CFS) at baseline and examined the cross-sectional association between antihypertensive category (inhibiting, stimulating, and mixed) and any cognitive impairment using a multivariable logistic regression, adjusting for the same covariates as the primary model.

We also conducted a secondary analysis to explore associations between individual antihypertensive sub-classes and the outcome of any cognitive impairment. To do so, we examined all possible antihypertensive sub-class combinations within the 'stimulating' categorization, which included thiazide only, dihydropyridine CCB only, ARB only, thiazide and dihydropyridine CCB, thiazide and ARB, dihydropyridine CCB and ARB, and thiazide, dihydropyridine CCB, and ARB. Each of these antihypertensive sub-class groups was compared to ACE-inhibitor only users, which was the most common 'inhibiting' sub-class used. The adjusted model included the same variables as the primary analysis.

We conducted an exploratory analysis using multistate modeling, given the high rate of death in NH residents. We examined transitions using a multistate model, which accounts for the competing risk of death. The model included the following 3 states: cognitively normal, any cognitive impairment, and death. We then conducted transition-specific Cox regression models, with follow-up time from nursing home admission as time scale, for each of the 3 states. We used the "msaj" command, a part of the Stata package "multistate", to calculate the non-parametric Aalen-Johansen estimates of state occupation probabilities. To assess the robustness of our results, we also conducted a sensitivity analysis redefining our outcome as moderately impaired (CFS=3) or severely impaired (CFS=4). Finally, to better understand changes in antihypertensive use after NH admission, we compared antihypertensive categories (i.e., stimulating, inhibiting, or mixed) at week 1 vs. week 2, week 3, week 4, 60 days, and 90 days. The main risk for exposure misclassification in this prevalent user design is when a resident switched from angiotensin II type 2 and 4 receptor stimulating antihypertensives only to inhibiting only (and vice versa).

## RESULTS

Of the 5,047 residents administered an antihypertensive of interest within the first week of NH admission, 2,927 (58.0%) used exclusively 'inhibiting' antihypertensives, 548 (10.9%) used exclusively 'stimulating' antihypertensives, and 1,572 (31.1%) used both. Characteristics of residents by the 3 antihypertensive categories are listed in Table 1 (mean age, 74.3 years; standard deviation, 7.9 years; 2.6% female; 75.4% white). Compared to the group using 'inhibiting' antihypertensives, the group using 'stimulating' and 'mixed' antihypertensive regimens had higher proportions of Black residents and higher first week average SBP values. Conversely, the group using 'stimulating' antihypertensives had a lower proportion of residents with coronary heart disease, heart failure, and atrial fibrillation, as compared to the groups using 'inhibiting' and 'mixed' antihypertensive regimens.

Over an average of 5.4 months of follow-up, any cognitive impairment occurred among 69.7% (N=382) of prevalent users of regimens containing exclusively 'stimulating' antihypertensives, 74.5% (N=2181) of prevalent users of regimens containing exclusively

'inhibiting' antihypertensives, and 74.5% (N=1171) of prevalent users of 'mixed' regimens. Multivariable Cox regression analyses are presented in Table 2. Prevalent use of regimens containing exclusively angiotensin II receptor type 2 and 4-'stimulating' antihypertensives was associated with a lower risk of any incident cognitive impairment as compared to prevalent use of regimens containing exclusively 'inhibiting' antihypertensives (HR 0.83, 95% CI 0.74-0.93). Results for the comparison between 'mixed' vs. 'inhibiting' regimens were in the same direction but not statistically significant (HR 0.96, 95% CI 0.88-1.06). Results were consistent using an IPTW-weighted Cox regression model ('stimulating' only: HR 0.78, 95% CI 0.65-0.94, 'mixed': 0.90, 95% CI 0.80-1.02; 'inhibiting' only: *reference*) (**Supplementary Table X**). The cross-sectional sensitivity analysis (including those with baseline cognitive impairment per the CFS) resulted in point estimates in the direction of a protective association for both 'stimulating' and 'mixed' antihypertensive regimens with any cognitive impairment (Supplementary Table 1).

Secondary analysis of individual antihypertensive sub-classes showed a lower risk of any incident cognitive impairment among those residents using a thiazide and ARB combination as compared to only an ACE-inhibitor (HR 0.64, 95% CI 0.42-0.98), as well as among those using only a thiazide diuretic as compared to only an ACE-inhibitor (HR 0.82, 95% CI 0.66-1.01) (Table S2).

Transition probabilities among the 3 states (no cognitive impairment or death, any cognitive impairment, and death) are presented in Supplementary Figures 1 and 2. Of the 5,047 cognitively intact residents, 74.0% (N=3,734) developed any cognitive impairment, and 24.6% (N=1,244) died within the NH stay. Most deaths were among residents who experienced any cognitive impairment (N=959, 77.1% of 1244 deaths). Use of only angiotensin II receptor type 2 and 4-'stimulating' antihypertensives was in the direction of a protective association for the transition from a healthy state to death (HR 0.65, 95% CI 0.42-1.01) (Table 3). However, residents using angiotensin II receptor type 2 and 4-'stimulating' antihypertensives did not differ from the other 2 antihypertensive categories for the transition from any cognitive impairment to death.

Results were robust to sensitivity analysis. Prevalent use of regimens containing exclusively angiotensin II receptor type 2 and 4-'stimulating' antihypertensives was associated with a lower risk of any incident moderate/severe cognitive impairment as compared to prevalent use of regimens containing exclusively 'inhibiting' antihypertensives (HR 0.84, 95% CI 0.75-0.95) (**Supplementary Table X**). Examining the prevalence of residents switching from angiotensin II type 2 and 4 receptor stimulating antihypertensives only to inhibiting only at the most distant time points (representing the highest prevalence) – 90 days vs. week 1 – resulted in the following: inhibiting-to-stimulating = 13/2927 (0.44%); stimulating-to-inhibiting = 16/548 (2.92%) (Supplementary Table 3).

## DISCUSSION

In this observational cohort study of VA long-term care residents, prevalent use of medication regimens containing exclusively angiotensin II receptor type 2 and 4-'stimulating' vs. 'inhibiting' antihypertensives was associated with a 17% lower risk of

incident cognitive impairment, over an average of 5.4 months of follow-up. Results were independent of SBP, cardiovascular risk factors, and sociodemographics, and robust to a cross-sectional sensitivity analysis. Secondary analyses suggest that users of combined treatment with a thiazide diuretic and an ARB, as compared to monotherapy with an ACE-inhibitor, had lower rates of incident cognitive impairment. However, these results from secondary analyses should be viewed as hypothesis-generating due to small sample sizes. Furthermore, the observed lower risk of incident cognitive impairment among prevalent users of angiotensin II receptor type 2 and 4-'stimulating' antihypertensives was not due to an increased risk of death. In fact, use of only angiotensin II receptor type 2 and 4-'stimulating' antihypertensives appeared marginally protective for the transition from a healthy state to death.

Given the high prevalence of hypertension, affecting more than 50% of US nursing home residents [16], even a small reduction in risk of cognitive impairment attained by prescribing certain antihypertensives could have a meaningful impact on the overall burden of cognitive impairment. Unfortunately, there is currently insufficient evidence to recommend prescribing certain classes of antihypertensives to reduce the risk of cognitive impairment [1]. Moreover, there is little evidence to guide antihypertensive prescribing for nursing home residents in general due to exclusion of frail and disabled older adults from landmark clinical trials of hypertension [3,13]. Additional observational research in larger, representative samples – using a new-user design – with validated cognitive outcomes could provide a useful replication. At the same time, our results align with findings from a small (n=176), randomized trial that compared the ARB, candesartan ('stimulating'), to the ACEI, lisinopril ('inhibiting'), in older adults with mild cognitive impairment (MCI). After 12-months, candesartan led to improvements in executive function and episodic memory as compared with lisinopril [17].

The results of the current analysis are also consistent with a secondary analysis of data from the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial, which found that prevalent users of only 'stimulating' antihypertensives had a 45% lower risk of incident dementia as compared to users of only 'inhibiting' antihypertensives over 6.7 years of follow-up [12]. It is important to note that we used a broad outcome measure (incident mild, moderate, or severe cognitive impairment per the CFS) in the current study, and had a short follow-up period given the high prevalence of cognitive impairment and death in long-term care settings. In fact, nearly 75% of residents developed cognitive impairment, and almost 25% died during their nursing home stay. This rate of cognitive impairment (as measured by the CFS) is consistent with previous findings from Thomas et al, who reported a prevalence of 72% of long-stay residents experiencing any cognitive impairment using the CFS [15]. However, the CFS has not been validated against widely used measures of cognitive impairment (e.g., MoCA); future work is needed to better elucidate the psychometric properties of the CFS. Moreover, the quality of data collected via MDS likely varies and could lead to CFS measurement error. Any measurement error is unlikely to differentially vary by antihypertensive medication use, though.

Taken together, these findings from observational data provide support for antihypertensive 'repurposing' – i.e., using antihypertensive medications to reduce risk of cognitive

impairment beyond their BP-lowering effects. On a population level, shifting antihypertensive prescribing from inhibiting to stimulating regimens, while adhering to current hypertension guideline recommendations, could be a promising strategy to reduce the burden of cognitive impairment. This would mean shifting the treatment paradigm from ACE-Is to ARBs, reducing the amount of inappropriate beta-blocker usage in the absence coronary heart disease or heart failure with reduced ejection fraction, and increasing the amount of thiazide diuretic usage as first-line treatment for hypertension. Opportunities for such a shift in antihypertensive prescribing exist in long-term care. For example, Boockvar et al reported that long-term nursing homes residents treated for hypertension in the US in 2013 were less likely to start a new thiazide diuretic than any other first-line antihypertensive medication [13]. Importantly, this study reported no association between thiazide diuretic use and urinary incontinence or hospitalization. This national study also found that 22% of long-term nursing home residents were treated with a beta-blocker as a single antihypertensive, indicating potentially inappropriate use.

Multiple animal and human studies help explain possible underlying mechanisms for our results. A sizable volume of animal model [18-25] and human studies [26-29] support the overarching hypothesis that beyond effects on BP, antihypertensive drugs that increase activity at the angiotensin type 2 and 4 receptors provide greater brain protection compared with those that decrease activity. Numerous studies suggest a role for angiotensin-II and angiotensin-IV activity in protecting from ischemia or enhancing cerebral blood flow, especially via activity at angiotensin type 2 and, possibly, type 4 receptors [9,30-32]. Agonism at the angiotensin type 4 receptor may improve spatial memory processing [22,23,33,34]. Translating this mechanistic work to clinical practice, using existing antihypertensives, is an area of active research.

This study has several limitations. First, the VA is not representative of the US population of nursing home residents, with a disproportionately higher ratio of men to women. Our results should be interpreted in this context. Second, we understand that a new-user design is ideal for estimating medication effects outside of trials. However, the study question necessitated a prevalent-user design given the age of the sample and high baseline prevalence of antihypertensive use, which could introduce bias. More specifically, we were unable to determine duration of hypertension and prior antihypertensive use for our sample. We assessed the potential for exposure misclassification by examining antihypertensive use across our study timeframe, and we found that there was minimal switching between the two main exposure categories (i.e., only ‘stimulating’ and only ‘inhibiting’ antihypertensive use) from baseline to 90 days. Our active-comparator design and methods of covariate adjustment were used to mitigate these sources of bias, but we cannot rule out the possibility for unmeasured confounding. Compared to users of ‘stimulating’ antihypertensives, a greater proportion of users of ‘inhibiting’ antihypertensives had a history of atrial fibrillation, coronary heart disease, and heart failure. While we adjusted for these differences in multivariable modeling, residual confounding could remain. As such, our results should be interpreted as associative.

In conclusion, prevalent users of regimens containing exclusively antihypertensives that stimulate versus inhibit type 2 and 4 angiotensin II receptors had lower rates of incident

cognitive impairment. We cannot rule out the possibility of residual confounding. If replicated in randomized clinical trials, certain antihypertensives could be repurposed to reduce the risk of cognitive impairment.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

This work was supported by the National Institutes of Health (RF1AG062568). ZA Marcum was supported by the National Institute on Aging of the National Institutes of Health (K76AG059929). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The sponsor had no role in the design, methods, data collection, analysis, or preparation of this paper.

## REFERENCES

[1]. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396, 413–446. [PubMed: 32738937]

[2]. National Academies of Sciences, Engineering, and Medicine (2017). Preventing Cognitive Decline and Dementia: A Way Forward. Washington, DC: The National Academies Press. 10.17226/24782.

[3]. SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Erus G, Fine LJ, Gaussoin SA, Harris D, Hsieh MK, Johnson KC, Kimmel PL, Tamura MK, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nasrallah IM, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco MV, Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JT Jr, Wright CB (2019). Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA 321, 553–561. [PubMed: 30688979]

[4]. Brown MJ (2007). Renin: friend or foe? Heart 93, 1026–1033. [PubMed: 17488768]

[5]. Kaschina E, Namsolleck P, Unger T (2017). AT2 receptors in cardiovascular and renal diseases. Pharmacol Res 125, 39–47. [PubMed: 28694144]

[6]. Forrester SJ, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, Scalia R, Eguchi S (2018). Angiotensin II signal transduction: an update on mechanisms of physiology and pathophysiology. Physiol Rev 98, 1627–1738. [PubMed: 29873596]

[7]. Saavedra JM, Benicky J, Zhou J (2006). Mechanisms of the anti-ischemic effect of angiotensin II AT(1) receptor antagonists in the brain. Cell Mol Neurobiol 26, 1099–1111. [PubMed: 16636899]

[8]. Horiuchi M, Mogi M (2011). Role of angiotensin II receptor subtype activation in cognitive function and ischaemic brain damage. Br J Pharmacol 163, 1122–1130. [PubMed: 21175580]

[9]. Ho JK, Nation DA (2018). Cognitive benefits of angiotensin IV and angiotensin-(1–7): A systematic review of experimental studies. Neurosci Biobehav Rev 92, 209–225. [PubMed: 29733881]

[10]. Hamel E, Royea J, Ongali B, Tong XK (2016). Neurovascular and cognitive failure in Alzheimer's disease: benefits of cardiovascular therapy. Cell Mol Neurobiol 36, 219–232. [PubMed: 26993506]

[11]. Baranello RJ, Bharani KL, Padmaraju V, Chopa N, Lahiri DK, Greig NH, Pappolla MA, Sambamurti K (2015). Amyloid-beta protein clearance and degradation (ABCD) pathways and their role in Alzheimer's disease. Curr Alzheimer Res 12, 32–46. [PubMed: 25523424]

[12]. van Dalen JW, Marcum ZA, Gray SL, Barthold D, van Charante EPM, van Gool WA, Crane PK, Larson EB, Richard E (2021). Association of angiotensin II–stimulating antihypertensive use and dementia risk: post hoc analysis of the PreDIVA trial. Neurology 96, e67–e80. [PubMed: 33154085]

[13]. Boockvar KS, Song W, Lee S, Intrator O (2020). Comparing outcomes between thiazide diuretics and other first-line antihypertensive drugs in long-term nursing home residents. Clin Ther 42, 583–591. [PubMed: 32229030]

[14]. Odden MC, Lee SJ, Steinman MA, Rubinsky AD, Graham L, Jing B, Fung K, Marcum ZA, Peralta CA (2021). Deprescribing blood pressure treatment in long-term care residents. J Am Med Dir Assoc S1525-8610(21)00647–2. doi: 10.1016/j.jamda.2021.07.009

[15]. Thomas KS, Dosa D, Wysocki A, Mor V (2017). The Minimum Data Set 3.0 Cognitive Function Scale. Med Care 55, e68–e72. [PubMed: 25763665]

[16]. Moore KL, Boscardin WJ, Steinman MA, Schwartz JB (2012). Age and sex variation in prevalence of chronic medical conditions in older residents of U.S. nursing homes. J Am Geriatr Soc 60, 756–764. [PubMed: 22463062]

[17]. Hajjar I, Okafor M, McDaniel D, Obideen M, Dee E, Shokouhi M, Quyyumi AA, Levey A, Goldstein F (2020). Effects of candesartan vs lisinopril on neurocognitive function in older adults with executive mild cognitive impairment: a randomized clinical trial. JAMA Netw Open 3, e2012252. [PubMed: 32761160]

[18]. Faure S, Chapot R, Tallet D, Javellaud J, Achard JM, Oudart N (2006). Cerebroprotective effect of angiotensin iv in experimental ischemic stroke in the rat mediated by AT(4) receptors. J Physiol Pharmacol 57, 329–342. [PubMed: 17033088]

[19]. Hamai M, Iwai M, Ide A, Tomochika H, Tomono Y, Mogi M, Horiuchi M (2006). Comparison of inhibitory action of candesartan and enalapril on brain ischemia through inhibition of oxidative stress. Neuropharmacology 51, 822–828. [PubMed: 16824557]

[20]. Iwai M, Inaba S, Tomono Y, Kanno H, Iwanami J, Mogi M, Horiuchi M (2008). Attenuation of focal brain ischemia by telmisartan, an angiotensin II type 1 receptor blocker, in atherosclerotic apolipoprotein E-deficient mice. Hypertens Res 31, 161–168. [PubMed: 18360031]

[21]. Iwai M, Liu H-W, Chen R, Ide A, Okamoto S, Hata R, Sakanaka M, Shiuchi T, Horiuchi M (2004). Possible inhibition of focal cerebral ischemia by angiotensin ii type 2 receptor stimulation. Circulation 110, 843–848. [PubMed: 15289370]

[22]. Lee J, Albiston AL, Allen AM, Mendelsohn FAO, Ping SE, Barrett GL, Murphy M, Morris MJ, McDowall SG, Chai SY (2004). Effect of I.C.V. injection of AT4 receptor ligands, NLE1-angiotensin IV and LVV-hemorphin 7, on spatial learning in rats. Neuroscience 124, 341–349. [PubMed: 14980384]

[23]. Li J, Culman J, Hörtnagl H, Zhao Y, Gerova N, Timm M, Blume A, Zimmermann M, Seidel K, Dirnagl U, Unger T (2005). Angiotensin AT2 receptor protects against cerebral ischemia-induced neuronal injury. FASEB J 19, 617–619. [PubMed: 15665034]

[24]. Lu Q, Zhu YZ, Wong PTH (2005). Neuroprotective effects of candesartan against cerebral ischemia in spontaneously hypertensive rats. Neuroreport 16, 1963–1967. [PubMed: 16272888]

[25]. Wang J, Ho L, Chen L, Zhao Z, Zhao W, Qian X, Humala N, Seror I, Bartholomew S, Rosendorff C, Pasinetti GM (2007). Valsartan lowers brain β-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. J Clin Invest 117, 3393–3402. [PubMed: 17965777]

[26]. Boutitie F, Oprisiu R, Achard JM, Mazouz H, Wang J, Messerli FH, Gueyffier F, Fournier A (2007). Does a change in angiotensin II formation caused by antihypertensive drugs affect the risk of stroke? A meta-analysis of trials according to treatment with potentially different effects on angiotensin II. J Hypertens 25, 1543–1553. [PubMed: 17620946]

[27]. Epstein BJ, Gums JG (2005). Can the renin-angiotensin system protect against stroke? A focus on angiotensin II receptor blockers. Pharmacotherapy 25, 531–539. [PubMed: 15977915]

[28]. Hajjar I, Brown L, Mack WJ, Chui H (2012). Impact of angiotensin receptor blockers on Alzheimer disease neuropathology in a large brain autopsy series. Arch Neurol 69, 1632–1638. [PubMed: 22964777]

[29]. Hajjar I, Levey A (2015). Association between angiotensin receptor blockers and longitudinal decline in tau in mild cognitive impairment. JAMA Neurol 72, 1069–1070. [PubMed: 26368351]

[30]. Braszko JJ, Walesiuk A, Wielgat P (2006). Cognitive effects attributed to angiotensin II may result from its conversion to angiotensin IV. J Renin Angiotensin Aldosterone Syst 7, 168–174. [PubMed: 17094054]

[31]. Saavedra JM, Benicky J, Zhou J (2006). Mechanisms of the anti-ischemic effect of angiotensin II AT(1) receptor antagonists in the brain. Cell Mol Neurobiol 26, 1099–1111. [PubMed: 16636899]

[32]. Chai SY, Bastias MA, Clune EF, Matsacos DJ, Mustafa T, Lee JH, McDowall SG, Paxinos G, Mendelsohn FA, Albiston AL (2000). Distribution of angiotensin IV binding sites (AT4 receptor) in the human forebrain, midbrain and pons as visualised by in vitro receptor autoradiography. J Chem Neuroanat 20, 339–348. [PubMed: 11207430]

[33]. Pederson ES, Krishnan R, Harding JW, Wright JW (2001). A role for the angiotensin AT4 receptor subtype in overcoming scopolamine-induced spatial memory deficits. Regul Pept 102, 147–156. [PubMed: 11730987]

[34]. Wright JW, Stubley L, Pederson ES, Kramár EA, Hanesworth JM, Harding JW (1999). Contributions of the brain angiotensin IV–AT4 receptor subtype system to spatial learning. J Neurosci 19, 3952–3961. [PubMed: 10234025]

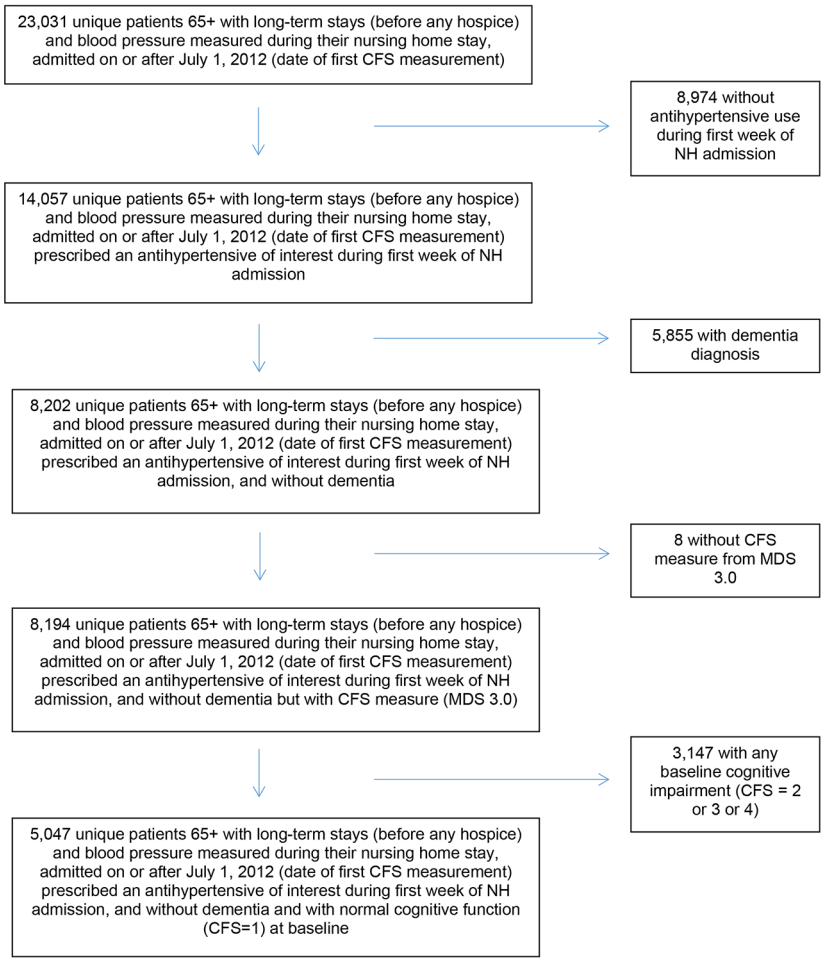


**Figure 1. Flow diagram of study population**

*Abbreviations*: CFS: cognitive function scale; MDS: Minimum Data Set; NH: nursing home

**Table 1.**

Characteristics of VA nursing home residents with no cognitive impairment, by blood pressure lowering medication regimen at admission (2012-2019)

| | **Inhibiting*** **N=2927** | **Stimulating†** **N=548** | **Mixed‡** **N=1572** |
|---|---|---|---|
| Age at NH admission (years) | 74.6 (8.0) | 74.8 (8.4) | 73.6 (7.6) |
| Age groups | - | - | - |
| 65-69 years | 1,020 (34.9%) | 205 (37.4%) | 605 (38.5%) |
| 70-74 years | 741 (25.3%) | 126 (23.0%) | 411 (26.2%) |
| 75-79 years | 394 (13.5%) | 61 (11.1%) | 221 (14.1%) |
| 80-84 years | 335 (11.5%) | 58 (10.6%) | 150 (9.5%) |
| 85-89 years | 257 (8.8%) | 57 (10.4%) | 106 (6.7%) |
| 90+ years | 180 (6.2%) | 41 (7.5%) | 79 (5.0%) |
| Female | 70 (2.4%) | 24 (4.4%) | 38 (2.4%) |
| Race | - | - | - |
| White | 2,356 (80.5%) | 361 (65.9%) | 1,089 (69.3%) |
| Black | 352 (12.0%) | 124 (22.6%) | 365 (23.2%) |
| Asian/Pacific Islander | 33 (1.1%) | 13 (2.4%) | 18 (1.2%) |
| American Indian | 16 (0.6%) | 1 (0.2%) | 10 (0.6%) |
| Multiple races | 20 (0.7%) | 7 (1.3%) | 14 (0.9%) |
| Missing | 150 (5.1%) | 42 (7.7%) | 76 (4.8%) |
| Ethnicity | - | - | - |
| Not Hispanic or unknown | 2,806 (95.9%) | 515 (94.0%) | 1,491 (94.9%) |
| Hispanic | 121 (4.1%) | 33 (6.0%) | 81 (5.2%) |
| Fiscal year cycle of NH Admission | - | - | - |
| FY2011 (July-September)-FY2012 | 106 (3.6%) | 12 (2.2%) | 53 (3.4%) |
| FY2013-FY2014 | 867 (29.6%) | 139 (25.4%) | 459 (29.2%) |
| FY2015-FY2016 | 939 (32.1%) | 174 (31.8%) | 426 (27.1%) |
| FY2017-FY2018 | 716 (24.5%) | 149 (27.2%) | 423 (26.9%) |
| FY2019 | 299 (10.2%) | 74 (13.5%) | 211 (13.4%) |
| Region | - | - | - |
| Continental | 431 (14.7%) | 82 (15.0%) | 222 (14.1%) |
| Midwest | 784 (26.8%) | 111 (20.3%) | 410 (26.1%) |
| North Atlantic | 757 (25.9%) | 152 (27.7%) | 423 (26.9%) |
| Pacific | 538 (18.4%) | 113 (20.6%) | 268 (17.1%) |
| Southeast | 403 (13.8%) | 90 (16.4%) | 249 (15.8%) |
| Missing | 14 (0.5%) | 0 (0%) | 0 (0%) |
| NH length of stay (days)§ | 272.6 (322.7) | 298.1 (378.3) | 280.1 (335.8) |
| Systolic BP (1st week, average) | 124.6 (14.5) | 132.5 (14.3) | 133.1 (15.4) |

| | **Inhibiting*** **N=2927** | **Stimulating†** **N=548** | **Mixed‡** **N=1572** |
|---|---|---|---|
| Diastolic BP (1st week, average) | 69.0 (7.6) | 71.7 (7.5) | 70.6 (7.6) |
| Baseline comorbidities | - | - | - |
| Hypertension | 2,622 (89.6%) | 523 (95.4%) | 1,523 (96.9%) |
| Diabetes | 1,698 (58.0%) | 278 (50.7%) | 1,053 (67.0%) |
| Coronary heart disease | 1,656 (56.6%) | 156 (28.5%) | 790 (50.3%) |
| Cerebrovascular disease | 761 (26.0%) | 115 (21.0%) | 488 (31.0%) |
| Heart failure | 1,504 (51.4%) | 147 (26.8%) | 703 (44.7%) |
| Atrial fibrillation | 1,203 (41.1%) | 98 (17.9%) | 430 (27.4%) |
| Renal failure | 1,071 (36.6%) | 212 (38.7%) | 750 (47.7%) |
| BMI at NH admission | 30.9 (9.5) | 30.4 (10.6) | 31.7 (9.0) |
| BMI categories | - | - | - |
| 18.5-24.9 | 638 (21.8%) | 110 (20.1%) | 280 (17.8%) |
| <18.5 | 50 (1.7%) | 16 (2.9%) | 19 (1.2%) |
| 25.0-29.9 | 828 (28.3%) | 172 (31.4%) | 421 (26.8%) |
| 30+ | 1,276 (43.6%) | 213 (38.9%) | 781 (49.7%) |
| Missing | 135 (4.6%) | 37 (6.8%) | 71 (4.5%) |
| "Other" antihypertensives‖ | 1,258 (43.0%) | 162 (29.6%) | 705 (44.9%) |
| Number of antihypertensives (1st week) | 1.86 (0.87) | 1.59 (0.75) | 2.98 (0.95) |

*Inhibiting defined as use of angiotensin-converting enzyme inhibitors, ß-blockers, and/or non-dihydropyridine calcium channel blockers.

†Stimulating defined as use of angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and/or thiazides.

‡Mixed defined as use of at least one inhibiting and at least one stimulating antihypertensive.

§NH length of stay defined as number of days between NH admission and discharge.

‖Other antihypertensives included loop diuretics, central alpha-blockers, vasodilators, and potassium-sparing diuretics.

*Note*: For race and BMI, separate categories of "missing" were used in regression analysis.

*Abbreviations*: Ang: angiotensin; BMI: body mass index; BP: blood pressure; CFS: Cognitive Function Scale; FY: fiscal year; NH: nursing home; VA: Veterans Affairs;

**Table 2.**

Adjusted Cox regression models for VA nursing home residents using angiotensin-II receptor type 2 and 4 stimulating only or both stimulating and inhibiting ("mixed") antihypertensive regimens as compared to those using inhibiting regimens only

| | **Outcome: Time to first cognitive impairment** | |
|---|---|---|
| **Antihypertensive categories** | **HR (95%CI)** | ***P*** |
| **Primary analysis** * | - | - |
| Inhibiting only† (*Reference*) (N=2927) | 1.0 | |
| Stimulating only‡ (N=548) | 0.83 (0.74-0.93) | <0.01 |
| Mixed§ (N=1572) | 0.96 (0.88-1.06) | 0.44 |
| Time to any cognitive impairment (per CFS) in days (SD): inhibiting, 91.4 (131.9); stimulating, 118.4 (198.7); mixed, 93.6. (149.1) | | |

*Model adjusted for sex, race, fiscal year, district, other antihypertensives, number of antihypertensives, systolic blood pressure, diastolic blood pressure, diabetes, atrial fibrillation, heart failure, coronary heart disease, cerebral vascular disease, BMI, renal failure

†Inhibiting defined as use of angiotensin-converting enzyme inhibitors, ß-blockers, and/or non-dihydropyridine calcium channel blockers.

‡Stimulating defined as use of angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and/or thiazides.

§Mixed defined as use of at least one inhibiting and at least one stimulating antihypertensive.

*Abbreviations*: ACE: angiotensin converting enzyme; Ang: angiotensin; ARB: angiotensin receptor type 1 blocker; CI: confidence interval; HR: hazard ratio

**Table 3.**

Transition-specific adjusted* Cox regression models

| | Time to any cognitive impairment | | Time to death (without interim cognitive impairment) | | Time from any cognitive impairment to death | |
|---|---|---|---|---|---|---|
| **Antihypertensive categories†** | **HR (95% CI)** | ***P*** | **HR (95%CI)** | ***P*** | **HR (95%CI)** | ***P*** |
| Inhibiting only | 1.0 | - | 1.0 | - | 1.0 | - |
| Stimulating only | 0.83 (0.74-0.93) | <0.01 | 0.65 (0.42-1.01) | 0.06 | 1.14 (0.92-1.41) | 0.24 |
| Mixed | 0.96 (0.88-1.06) | 0.44 | 0.93 (0.64-1.35) | 0.71 | 0.98 (0.81-1.19) | 0.86 |

*Each model adjusted for sex, race, fiscal year of nursing home admission, district, other antihypertensives, number of antihypertensives received in the first week, systolic and diastolic blood pressure (averaged in the first week), baseline comorbidities (diabetes, atrial fibrillation, heart failure, coronary heart disease, cerebral vascular disease and renal failure), and baseline BMI.

†Inhibiting defined as use of angiotensin-converting enzyme inhibitors, ß-blockers, and/or non-dihydropyridine calcium channel blockers. Stimulating defined as use of angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and/or thiazides. Mixed defined as use of at least one inhibiting and at least one stimulating antihypertensive.