Published in final edited form as:
*JAMA Intern Med*. 2014 April ; 174(4): 588–595. doi:10.1001/jamainternmed.2013.14764.

# Antihypertensive Medications and Serious Fall Injuries in a Nationally Representative Sample of Older Adults

**Mary E. Tinetti, MD**, **Ling Han, MD, PhD**, **David S. H. Lee, PharmD, PhD**, **Gail J. McAvay, PhD**, **Peter Peduzzi, PhD**, **Cary P. Gross, MD**, **Bingqing Zhou, PhD**, and **Haiqun Lin, PhD**
Section of Geriatrics, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut (Tinetti, Han, McAvay, Gross); Yale School of Public Health, New Haven, Connecticut (Tinetti, Peduzzi, Zhou, Lin); Oregon State University, Oregon Health & Science University, College of Pharmacy, Portland (Lee).

## Abstract

**IMPORTANCE—**The effect of serious injuries, such as hip fracture and head injury, on mortality and function is comparable to that of cardiovascular events. Concerns have been raised about the risk of fall injuries in older adults taking antihypertensive medications. The low risk of fall injuries reported in clinical trials of healthy older adults may not reflect the risk in older adults with multiple chronic conditions.

**OBJECTIVE—**To determine whether antihypertensive medication use was associated with experiencing a serious fall injury in a nationally representative sample of older adults.

**DESIGN, PARTICIPANTS, AND SETTING—**Competing risk analysis as performed with propensity score adjustment and matching in the nationally representative Medicare Current Beneficiary Survey cohort during a 3-year follow-up through 2009. Participants included 4961 community-living adults older than 70 years with hypertension.

**EXPOSURES—**Antihypertensive medication intensity based on the standardized daily dose for each antihypertensive medication class that participants used.



**Corresponding Author:** Mary E. Tinetti, MD, Section of Geriatrics, Department of Internal Medicine, Yale School of Medicine, 333 Cedar St, PO Box 208025, New Haven, CT 06520-8025 (mary.tinetti@yale.edu).

**Author Contributions**: Drs Han and McAvay had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design*: Tinetti, Han, Lee, Gross.
*Acquisition of data*: McAvay.
*Analysis and interpretation of data*: Tinetti, Han, Lee, McAvay, Peduzzi, Zhou, Lin.
*Drafting of the manuscript*: Tinetti, Lee, Peduzzi.
*Critical revision of the manuscript for important intellectual content*: Han, McAvay, Peduzzi, Gross, Zhou, Lin.
*Statistical analysis*: Han, McAvay, Peduzzi, Zhou, Lin.
*Obtained funding*: Tinetti.
*Study supervision*: Tinetti.

**Conflict of Interest Disclosures**: Dr Gross reports receiving research funding from Medtronic (to help design a plan for sharing of patient-level trial data) and from 21st Century Oncology and being on the Scientific Advisory Board of Fair Health, Inc. No other disclosures were reported.

**MAIN OUTCOMES AND MEASURES—**Serious fall injuries, including hip and other major fractures, traumatic brain injuries, and joint dislocations, ascertained through Centers for Medicare & Medicaid Services claims.

**RESULTS—**Of the 4961 participants, 14.1% received no antihypertensive medications; 54.6% were in the moderate-intensity and 31.3% in the high-intensity antihypertensive groups. During follow-up, 446 participants (9.0%) experienced serious fall injuries, and 837 (16.9%) died. The adjusted hazard ratios for serious fall injury were 1.40 (95% CI, 1.03–1.90) in the moderate-intensity and 1.28 (95% CI, 0.91–1.80) in the high-intensity antihypertensive groups compared with nonusers. Although the difference in adjusted hazard ratios across the groups did not reach statistical significance, results were similar in the propensity score–matched subcohort. Among 503 participants with a previous fall injury, the adjusted hazard ratios were 2.17 (95% CI, 0.98–4.80) for the moderate-intensity and 2.31 (95% CI, 1.01–5.29) for the high-intensity antihypertensive groups.

**CONCLUSIONS AND RELEVANCE—**Antihypertensive medications were associated with an increased risk of serious fall injuries, particularly among those with previous fall injuries. The potential harms vs benefits of antihypertensive medications should be weighed in deciding to continue treatment with antihypertensive medications in older adults with multiple chronic conditions.

Most persons older than 70 years have hypertension.[1] Blood pressure control is a central component of myocardial infarction and stroke risk reduction guidelines.[2–4] A recent multispecialty task force, however, raised concerns about the risk of falls associated with antihypertensive medications in older adults.[5] Decisions concerning which medications to initiate, continue, or increase in older patients with multiple coexisting conditions should take into account the likelihood of benefit and harm.

Randomized clinical trials (RCTs) of older adults show a relative risk reduction of 28% in cardiovascular events with antihypertensive treatment, reducing the absolute risk of cardiovascular events from 15.3 to 11.0 per 100 RCT participants within 4½ years.[6] Participants in these RCTs suffered from fewer comorbid conditions than an age-matched clinical population.[5,7,8] It remains to be determined whether the large proportion of older adults with multiple chronic conditions accrue the cardiovascular benefit from antihypertensive treatment experienced by relatively healthy participants in RCTs. Optimal levels are unclear in older adults, with studies showing inverse relationships between extent of blood pressure lowering and cardiovascular benefit.[9–14]

As for potential harms of antihypertensive medications, individuals with coexisting conditions may be at greater risk of experiencing harmful effects than the healthy participants in RCTs. Determining whether antihypertensive medications increase the risk of serious fall injuries is particularly important because serious fall injuries, such as traumatic brain injury and hip fracture, have an effect on function and mortality similar to that of cardiovascular events, such as myocardial infarction and stroke. Furthermore, older adults with hypertension vary in what is most important when presented the trade-off between preventing strokes and myocardial infarctions or avoiding medication-related symptoms and serious fall injuries.[15]

Several lines of investigation suggest that antihypertensive medications may increase risk of falls and fall injuries. Risk factors for falls and fractures, such as balance and gait impairment, dizziness, and postural hypotension, are among the most common adverse effects of medications, including antihypertensive medications.[16–20] A meta-analysis of observational studies showed a 24% increased odds of falling associated with use of antihypertensive agents.[21] The studies included in the meta-analysis varied in the extent of adjustment for confounding factors and ascertainment of fall-related outcomes. Several studies assessing the association between initiating different antihypertensive medications and the occurrence of falls and fractures produced variable results.[21–26] The effect of ongoing antihypertensive use on risk of serious fall injuries is also unclear.

The aim of the current study was to determine, in a nationally representative sample of older adults with hypertension, whether antihypertensive medication use was associated with an increased risk of experiencing a serious fall injury.

## Methods

### Study Design and Sample

The study was deemed exempt from review by the Yale University Human Investigation Committee because it involved existing, publically available, de-identified data. The study sample included participants enrolled from 2004 to 2007 in the Medicare Current Beneficiary Survey, a nationally representative sample of Medicare beneficiaries obtained using stratified multistage sampling from the Centers for Medicare & Medicaid Services enrollment file.[27] Eligibility criteria for the current study included age older than 70 years, community-living status at baseline, and status as a traditional Medicare beneficiary. Medicare Advantage beneficiaries were excluded because they lack health claims. Of the 6989 Medicare Current Beneficiary Survey members who met these eligibility criteria, 5124 (73.3%) had at least 2 Medicare inpatient, physician, or outpatient claims for hypertension. The 4961 participants (96.8%) with claims-based diagnosis of hypertension for whom medication data were available constituted the study cohort. Follow-up was continued for up to 3 years through 2009.

### Descriptive Data

Chronic conditions were ascertained from Medicare hospital, outpatient, and physician claims data. The Elixhauser comorbidity scale was computed based on the *International Classification of Diseases, Ninth Revision* codes from claims data.[28] Sociodemographic, behavioral, and functional data (basic and instrumental activities of daily living) were obtained by questionnaire during the Access to Care baseline interviews that took place 1 to 3 months before the beginning of follow-up.[27] Depression was defined from self-report questionnaire data or claims. Cognitive impairment or dementia was considered present if there were claims for dementia or cognitive disorder or self-reported memory loss and either trouble concentrating or difficulty making decisions that interfered with activities of daily living.

## Medication Data

Prescription medications were ascertained by direct observation during 4 in-person interviews in the year after enrollment. The antihypertensive medication classes included diuretics, renin-angiotensin system blockers (angiotensinconverting enzyme inhibitors and angiotensin receptor blockers), β-blockers (selective, nonselective, and α-β-blocker agents), calcium channel blockers (nondihydropyridines and dihydropyridines), centrally acting antiadrenergic agents, and other (ie, peripheral acting antiadrenergic agents or vasodilators).[4] Combination medications were included in all relevant classes. Each daily dose was converted to a standardized daily dose based on the corresponding defined daily dose (DDD) proposed by the World Health Organization International Working Group for Drug Statistics Methodology.[29] The daily antihypertensive medication exposure intensity (hereafter *antihypertensive intensity*) for each participant was derived by dividing the total DDD across all antihypertensive agents by the number of days under observation. We also calculated the number of antihypertensive medication classes (0, 1, 2, and ≥3) each participant used.

## Outcomes

*Serious fall injuries* were defined based on emergency department and inpatient claims as events with a fall-related E code (8800–8889) and an injury code for nonpathological skull, facial, cervical, clavicle, humeral, forearm, pelvic, hip, fibula, tibia, or ankle fractures (80000–80619, 8070–8072, 8080–8089, 81000–81419, 8180–8251, or 8270–8291), brain injury (85200–85239), or dislocation of the hip, knee, shoulder, or jaw (8300–83219, 83500–83513, or 83630–83660). In the absence of a fall-related E code, the event was considered a fall-related injury if there was an emergency department or inpatient claim for any of these serious injuries and there was no motor vehicle accident E code (8100–8199). These categories of injuries correlate well with self-report of a fall as the cause of the injury.[30] Death was ascertained from the Medicare vital status file.

## Statistical Analysis

Baseline characteristics were summarized using means and SDs or frequency and percentages. Antihypertensive intensity was trichotomized based on the distribution and clinical judgment as none (0 to <0.2 DDD), moderate (0.2–2.5 DDD), or high (>2.5 DDD). To control for confounding by indication, we estimated a propensity score (PS) using a cumulative logit regression model, with the 3-level antihypertensive intensity as an ordinal outcome.[31–33] The PS model included 36 covariates (Table 1) selected based on the literature and clinical judgment. After deriving the PS, we examined its distribution in the study population and checked the balance of each covariate across the 3 antihypertensive intensity groups using a cumulative logit model, comparable to the PS estimation model, before and after adjusting for the PS as a continuous covariate.[32–34]

We used proportional hazards models to examine the relationship between antihypertensive intensity groups and the study outcomes.[32,35] We used standard Cox proportional hazards regression to analyze mortality and a competing risk model using subdistribution hazards regression to analyze serious fall injury events, accounting for potential bias due to the high attrition from mortality.[33–38] In these analyses, deaths with no serious fall injury event

anytime during follow-up were treated as the competing event. We first fitted regression models with and without adjusting for a continuous PS and 21 a priori selected covariates (listed in Table 2). Although some of these covariates were used to estimate the PS, including them in the outcome models enabled us to control for residual confounding.[31] Hazard ratios and 95% CIs were estimated for the moderate- and high-intensity antihypertensive groups in reference to the no-antihypertensive group. Model fit and the proportional hazards assumptions were checked by examining Martingale residuals and cumulative incidence plots and by testing antihypertensive intensity through survival time interactions.[32,35,37]

We repeated the subdistribution proportional hazards regression model for the serious injury outcome in a more homogeneous subcohort assembled using a greedy matching algorithm based on the estimated PS.[32,39] With an 0.02 SD of the mean PS in the nonuser group as the caliper width, we matched each nonuser with at least 1 participant from the moderate- and high-intensity antihypertensive groups. The balance of covariates between groups was evaluated using standardized differences,[32,39] which contrast the group means of covariates in units of the pooled SDs of the comparison groups and enable assessment of the balance of covariates across groups with different sizes. A standardized difference less than 0.10 is considered well balanced.[32,39]

In secondary analyses, we repeated the models, substituting the number of antihypertensive medication classes (0, 1, 2, or ≥3) for antihypertensive intensity. Finally, we examined whether the association between antihypertensive intensity and serious fall injury varied by age, sex, and high baseline fall injury risk, defined as a claim for a fall injury in the year before enrollment.

We performed the competing risk analyses using a sub-distribution proportional hazards regression model.[36] To account for potential nonproportional hazards, we estimated time-averaged hazard ratios and their 95% CIs using the SAS macro %PSHREG with SAS v9.3 software (SAS Institute).[37,38] We estimated the competing risk analyses in the PS-matched subcohort using the R package crrSC (http://www.r-project.org), in which matching was accounted for as a clustering factor.[32] Differences were considered significant at $P < .05$ (2 tailed).

## Results

The mean age of the 4961 participants in the full cohort was 80.2 (6.8) years; 3050 (61.5%) were female. Characteristics of the 697 participants (14.1%) in the no-antihypertensive group, the 2711 (54.6%) in the moderate-intensity group, and the 1553 (31.3%) in the high-intensity group are presented in Table 1. Participants in the no-antihypertensive group differed from the 2 antihypertensive group participants on several characteristics; none of these differences were statistically significant after adjustment for PS (Table 1). The frequency of antihypertensive medication classes was 2809 (56.6%) for renin-angiotensin system blockers, 2691 (54.2%) for diuretics, 2277 (45.9%) for β-blockers, and 1695 (34.2%) for calcium channel blockers; 349 (7.0%) used other antihypertensive medication classes.

Among antihypertensive medication users, 1265 (28.3%) took 1 class, 1599 (35.8%) took 2 classes, and 1607 (35.9%) took at least 3 classes of antihypertensive medications.

Characteristics of the 2849 members of the PS-matched subcohort are also displayed in Table 1. The PS-matched sample included 662 (95.0%) of the no-antihypertensive, 1455 (53.7%) of the moderate-intensity, and 732 (47.1%) of the high-intensity groups. The 3 groups were well matched on all characteristics based on standardized differences (Table 1) except for a higher percentage of high-intensity users with a body mass index of at least 30 (calculated as weight in kilograms divided by height in meters squared) and a higher percentage of non-users with cognitive impairment.

During follow-up, 446 participants (9.0%) experienced a serious fall injury. These serious injuries included 107 hip fractures, 345 other major fractures in 312 persons, 72 major head injuries, and 16 major joint dislocations. Fifty-eight participants experienced more than 1 type of serious injury (eg, a hip and other fracture) with a fall.

A total of 837 participants (16.9%) died during follow-up, including 111 (24.9%) of the 446 participants who experienced a serious fall injury and 726 (16.1%) of the 4515 participants who did not.

In bivariate analysis, a serious fall injury was experienced by 52 participants (7.5%) in the no-antihypertensive group, 267 (9.8%) in the moderate-intensity group, and 127 (8.2%) in the high-intensity group ($\chi^2 = 5.69$; P = .058). In the PS-matched subcohort, 47 participants (7.1%) in the no-antihypertensive medication group, 125 (8.6%) in the moderateintensity group, and 62 (8.5%) in the high-intensity group ($\chi^2 = 8.32$; P = .08) had a serious fall injury.

In multivariate analysis that accounted for the competing risk of mortality, antihypertensive medication use was associated with an increased risk of experiencing a serious fall injury. Results for the full cohort and the PS-matched subcohort are shown in Table 2. In the full cohort, the adjusted hazard ratio was 1.40 (95% CI, 1.03–1.90) for moderate-intensity and 1.28 (95% CI, 0.91–1.80) for high-intensity users compared with no antihypertensive use. The adjusted 3-year cumulative incidence of serious fall injury events was 9.0% in the no-antihypertensive, 11.6% in the moderate-intensity, and 10.9% in the high-intensity groups.

No class of antihypertensive was associated with an increased risk of serious fall injuries, as shown in Table 2. We also looked at the relationship between the number of antihypertensive classes used and serious fall injuries. The adjusted hazard ratio was 1.30 (95% CI, 0.90–1.89) for 1 class, 1.37 (95% CI, 0.95–1.98) for 2 classes, and 1.17 (0.80–1.71) for 3 or more classes of antihypertensive medications compared with no antihypertensive use in the full cohort, with similar results in the PS-matched cohort.

In subgroup analyses, a fall injury in the prior year was associated with more than a doubling of the risk for subsequent serious fall injury with moderate- and high-intensity antihypertensive use compared with no antihypertensive use (Figure). The association between antihypertensive intensity and serious fall injury was similar in participants younger than 85 years and those 85 years or older and similar in men and women (Figure).

## Discussion

Antihypertensive medication use was associated with an increased risk of serious fall injuries in this representative sample of older adults with hypertension and multiple other conditions. Among the subgroup of persons with a fall injury in the prior year, those who received antihypertensive medications were more than twice as likely as those who did not to experience a subsequent serious fall injury, such as a hip fracture or serious head injury.

No particular antihypertensive class was associated with risk of fall injuries. Results from previous studies, most of which involved participants initiating rather than continuing antihypertensive treatment, are mixed.[21–26] For example, studies show both increased and decreased risk of falls or fractures after institution of thiazide diuretic treatment. The role of individual classes remains to be determined.

We did not find a linear dose-response relationship with either intensity or numbers of classes. Studies also show a Jshaped relationship between number of medications and degree of blood pressure lowering and reduction in cardiovascular events in older adults.[9–14] The estimates for moderate and high intensity are similar, suggesting that the J-shaped relationship may have occurred by chance. Because the low rate of falls reported in RCTs of healthy older adults may not reflect clinical practice, observational studies may better indicate expected rates of serious injury in representative samples of older adults. The evidence from observational studies has been mixed, but our findings are consistent with prior studies and meta-analyses.[21,40,41] In interpreting previous studies, it is important to consider the high frequency of deaths in this population.

The relationship among antihypertensive medications, serious fall injury, and death is complex. Although the proportion of participants who died was higher in those who had a serious fall injury than in those who did not, we do not have cause-of-death data to determine which participants died as a result of their fall injury. Studies have shown high mortality rates associated with fall-related hip fractures and traumatic brain injuries.[42,43] Previous analyses of this representative cohort showed a modest (21%–28%) decrease in total mortality associated with antihypertensive use[44] (M.E.T., unpublished data, 2014). Further study is needed to determine the net effect of antihypertensive medications on total and cause-specific mortality in representative populations of older adults.

To our knowledge, ours is the first study to evaluate the risk of the most serious fall injuries, such as traumatic brain injury or hip fracture, associated with prevalent antihypertensive medications. Although noninjurious falls and minor fall injuries are associated with morbidity, we limited our study to serious fall injuries, which are more clinically equivalent to the cerebrovascular and cardiovascular events that antihypertensive medications are prescribed to prevent.

Both hypertension and antihypertensive medications could affect fall injury risk through multiple mechanisms. Antihypertensive medications and blood pressure control may decrease the risk of falls through improved postural blood pressure or cognition, particularly executive function.[44–46] Conversely, risk factors for falls are among the most common adverse medication effects, including antihypertensive medications.[16–20,47,48] The increased

injury risk observed in the current study may reflect a trade-off between the beneficial and harmful effects of antihypertensive medications. Because blood pressure readings were not available, we could not determine whether blood pressure level or postural changes in blood pressure affected risk of fall injury independent of antihypertensive intensity or in interaction with it.

This study has strengths as well as limitations. The large, nationally representative cohort enhances the generalizability of results to the older adult population. The well-characterized cohort allowed us to account for many factors that affected propensity both to receive antihypertensive medications and to experience serious fall injuries. The combination of Medicare claims data, including *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes for injuries and external cause of injury codes (E codes), allowed us to reliably identify serious fall injuries in the cohort.[48] The use of competing risk analyses allowed us to account for the high rate of death in this representative elderly population. Conventional Cox proportional hazards regression models would have underestimated the risk of fall injuries in this population.[37,49]

We used both PS adjustment and PS matching to account for biases and confounding inherent in observational studies. Although the smaller sample size precluded finding statistical significance in the matched subcohort, results were similar with the two analytical approaches, supporting the validity of the findings. Results were also similar when we substituted number of medication classes for antihypertensive intensity. Despite adjustment for a wide array of confounding factors, however, we cannot exclude the possibility of unmeasured confounders and the possibility that persons who do not take antihypertensive medications may be inherently different from those who do.

We did not have information on time of onset of hypertension or duration of antihypertensive treatment. Inception cohorts have been recommended as one means of limiting bias in observational studies and assuring that the confounders are measured before initiation of treatment with medications,[50] but this was not feasible or appropriate for the current study. Because most older hypertensive adults have had hypertension and been receiving treatment for many years,[1] the clinical question is the likely benefit vs harm of continuing medications. Prevalent users are the appropriate participants to address this issue. Despite limitations and methodological challenges, the Medicare Current Beneficiary Survey cohort represents the patient population for whom the decision of whether to continue antihypertensive medications is relevant.

Although no single study is definitive and we cannot presume a cause-effect relationship between medication use and serious fall injury, results have potential clinical implications. The coexistence of multiple chronic conditions, as was seen in this nationally representative sample, puts older adults at risk for adverse consequences of medications used to treat each condition. It is important, therefore, to consider the effects of medications not only on the conditions for which the medications are indicated but also on coexisting conditions, including fall injury risk. The morbid effects associated with serious fall injuries, such as hip fracture and head injury, which are comparable to those imposed by myocardial infarction

and stroke, suggest that treatment decisions should be predicated on maximizing benefit and minimizing harm, preferably based on risk stratification.

Risk factors for fall injuries and cardiovascular events are available to inform this estimation, but further study is needed to determine which factors best distinguish persons most likely to accrue benefit greater than harm, including the effects on both function and mortality. The biases inherent in observational studies and the inappropriateness of extrapolating RCT results from healthy older adults to those with multiple chronic conditions strongly support performing an RCT involving a representative sample of older adults to acquire this evidence. In the meantime, the potential trade-off between serious fall injury and cardiovascular events and mortality suggests that each older adult's prevention priority should drive decision making.[15,51,52]

## Conclusions

The morbidity and mortality associated with serious injuries such as hip fracture and head injury are comparable to those associated with cardiovascular events. The low risk of fall injuries reported in clinical trials of healthy older adults may not reflect the risk in older adults with multiple chronic conditions. Although cause and effect cannot be established in this observational study and we cannot exclude confounding, antihypertensive medications seemed to be associated with an increased risk of serious fall injury compared with no antihypertensive use in this nationally representative cohort of older adults, particularly among participants with a previous fall injury. The potential harms vs benefits of antihypertensive medications should be weighed in deciding whether to continue antihypertensives in older adults with multiple chronic conditions.

## Acknowledgments

**Funding/Support**: This research was funded by the National Institute on Aging (grant R01 AG038528 and grant P30 AG021342 to the Yale Pepper Center).

**Role of the Sponsor**: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## REFERENCES

1. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health and Nutrition Examination Survey, 2001 to 2010. Circulation. 2012; 126(17):2105–2114. [PubMed: 23091084]
2. Smith SC Jr, Benjamin EJ, Bonow RO, et al. World Heart Federation; Preventive Cardiovascular Nurses Association. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011; 124(22): 2458–2473. [PubMed: 22052934]
3. Goldstein LB, Bushnell CD, Adams RJ, et al. American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42(2):517–584. [PubMed: 21127304]

4. Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289(19):2560–2572. [PubMed: 12748199]
5. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF Task Force. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation. 2011; 123(21):2434–2506. [PubMed: 21518977]
6. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev. 2009; (4):CD000028. [PubMed: 19821263]
7. Dhruva SS, Redberg RF. Variations between clinical trial participants and Medicare beneficiaries in evidence used for Medicare national coverage decisions. Arch Intern Med. 2008; 168(2):136–140. [PubMed: 18227358]
8. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007; 297(11):1233–1240. [PubMed: 17374817]
9. Vokó Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. J-shaped relation between blood pressure and stroke in treated hypertensives. Hypertension. 1999; 34(6):1181–1185. [PubMed: 10601115]
10. Ogihara T, Matsuoka H, Rakugi H. Practitioner's trial on the efficacy of antihypertensive treatment in elderly patients with hypertension II (PATE-Hypertension II study) in Japan. Geriatr Gerontol Int. 2011; 11(4):414–421. [PubMed: 21410854]
11. Denardo SJ, Gong Y, Nichols WW, et al. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. Am J Med. 2010; 123(8):719–726. [PubMed: 20670726]
12. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med. 2006; 144(12):884–893. [PubMed: 16785477]
13. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res. 2008; 31(12):2115–2127. [PubMed: 19139601]
14. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. Treatment of hypertension in patients 80 years and older: the lower the better? a meta-analysis of randomized controlled trials. J Hypertens. 2010; 28(7):1366–1372. [PubMed: 20574244]
15. Tinetti ME, McAvay G, Fried TR, et al. Health outcome priorities among competing cardiovascular, fall injury, and medication-related symptom outcomes. J Am Geriatr Soc. 2008; 56(8):1409–1416. [PubMed: 18662210]
16. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. N Engl J Med. 2003; 348(16):1556–1564. [PubMed: 12700376]
17. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA. 2003; 289(9):1107–1116. [PubMed: 12622580]
18. Gray SL, Mahoney JE, Blough DK. Adverse drug events in elderly patients receiving home health services following hospital discharge. Ann Pharmacother. 1999; 33(11):1147–1153. [PubMed: 10573310]
19. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc. 2004; 52(8):1349–1354. [PubMed: 15271125]
20. Gray SL, Sager M, Lestico MR, Jalaluddin M. Adverse drug events in hospitalized elderly. J Gerontol A Biol Sci Med Sci. 1998; 53(1):M59–M63. [PubMed: 9467435]
21. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009; 169(21):1952–1960. [PubMed: 19933955]

22. Gribbin J, Hubbard R, Gladman JRF, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: population-based case-control study. Age Ageing. 2010; 39(5):592–597. [PubMed: 20650874]
23. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. Arch Intern Med. 2012; 172(22):1739–1744. [PubMed: 23165923]
24. Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: self-controlled case series. Pharmacoepidemiol Drug Saf. 2011; 20(8):879–884. [PubMed: 21744415]
25. Berry SD, Zhu Y, Choi H, Kiel DP, Zhang Y. Diuretic initiation and the acute risk of hip fracture. Osteoporos Int. 2013; 24(2):689–695. [PubMed: 22790610]
26. Solomon DH, Mogun H, Garneau K, Fischer MA. Risk of fractures in older adults using antihypertensive medications. J Bone Miner Res. 2011; 26(7):1561–1567. [PubMed: 21312268]
27. Medicare Current Beneficiary Survey (MCBS). [Accessed August 15, 2013] http://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/index.html
28. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998; 36(1):8–27. [PubMed: 9431328]
29. Wessling A, Boëthius G. Measurement of drug use in a defined population: evaluation of the defined daily dose (DDD) methodology. Eur J Clin Pharmacol. 1990; 39(3):207–210. [PubMed: 2257853]
30. Tinetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury during falls by older persons in the community. J Am Geriatr Soc. 1995; 43(11):1214–1221. [PubMed: 7594154]
31. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998; 17(19):2265–2281. [PubMed: 9802183]
32. Faries, DE.; Leon, AC.; Haro Maria, J.; Obenchain, RL., editors. Analysis of Observational Health Care Data Using SAS. Cary, NC: SAS Institute; 2010.
33. Leon AC, Hedeker D, Teres JJ. Bias reduction in effectiveness analyses of longitudinal ordinal doses with a mixed-effects propensity adjustment. Stat Med. 2007; 26(1):110–123. [PubMed: 16345035]
34. Allison, PD. Logistic Regression Using the SAS System: Theory and Application. Cary, NC: SAS Institute Inc; 1999.
35. Hosmer, DWJ.; Lemeshow, S., editors. Applied Survival Analysis: Regression Modeling of Time to Event Data. New York, NY: John Wiley & Sons; 1999.
36. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94(446):496–509.
37. Kohl, M.; Heinze, G. Vienna, Austria: Medical University of Vienna; 2012. PSHREG: A SAS Macro for Proportional and Nonproportional Subdistribution Hazards Regression With Competing Risk Data. Technical report 08/2012
38. Xu R, O'Quigley J. Estimating average regression effect under non-proportional hazards. Biostatistics. 2000; 1(4):423–439. [PubMed: 12933565]
39. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med. 2008; 27(12):2037–2049. [PubMed: 18038446]
40. Rozenfeld S, Camacho LA, Veras P. Medication as a risk factor for falls in older women in Brazil. Rev Panam Salud Publica. 2003; 13(6):369–375. [PubMed: 12880517]
41. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis, II: cardiac and analgesic drugs. J Am Geriatr Soc. 1999; 47(1):40–50. [PubMed: 9920228]
42. Tajeu GS, Delzell E, Smith W, et al. Death, debility, and destitution following hip fracture. J Gerontol A Biol Sci Med Sci. 2013
43. Coronado VG, Xu L, Basavaraju SV, et al. Centers for Disease Control and Prevention (CDC). Surveillance for traumatic brain injury-related deaths—United States, 1997–2007. MMWR Surveill Summ. 2011; 60(5):1–32. [PubMed: 21544045]

44. Kuo H-K, Sorond F, Iloputaife I, Gagnon M, Milberg W, Lipsitz LA. Effect of blood pressure on cognitive functions in elderly persons. J Gerontol A Biol Sci Med Sci. 2004; 59(11):1191–1194. [PubMed: 15602074]
45. Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study. J Am Geriatr Soc. 2011; 59(3):383–389. [PubMed: 21391928]
46. Hajjar I, Hart M, Chen YL, et al. Effect of antihypertensive therapy on cognitive function in early executive cognitive impairment: a double-blind randomized clinical trial. Arch Intern Med. 2012; 172(5):442–444. [PubMed: 22412114]
47. Agostini JV, Han L, Tinetti ME. The relationship between number of medications and weight loss or impaired balance in older adults. J Am Geriatr Soc. 2004; 52(10):1719–1723. [PubMed: 15450051]
48. Barrett, M.; Steiner, C. [Accessed September 14, 2013] Addendum to healthcare cost and utilization project (HCUP) E code evaluation report (updated for 2009). HCUP Methods Series Report 2004–06. November 1, 2011. US Agency for Healthcare Research and Quality. http://www.hcup-us.ahrq.gov/reports/methods/2004_06_add_09.pdf
49. Zhou B, Fine J, Latouche A, Labopin M. Competing risks regression for clustered data. Biostatistics. 2012; 13(3):371–383. [PubMed: 22045910]
50. Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. Pharmacoepidemiol Drug Saf. 2013; 22(1):1–6. [PubMed: 23023988]
51. Fried TR, McGraw S, Agostini JV, Tinetti ME. Views of older persons with multiple morbidities on competing outcomes and clinical decision-making. J Am Geriatr Soc. 2008; 56(10):1839–1844. [PubMed: 18771453]
52. Fried TR, Tinetti ME, Towle V, O'Leary JR, Iannone L. Effects of benefits and harms on older persons' willingness to take medication for primary cardiovascular prevention. Arch Intern Med. 2011; 171(10):923–928. [PubMed: 21357797]

| Character | HR (95% CI) |
|---|---|
| **Age** | |
| **<85 y (n = 3918)** | |
| Moderate intensity | 1.41 (0.97-2.06) |
| High intensity | 1.39 (0.92-2.10) |
| **≥85 y (n = 1206)** | |
| Moderate intensity | 1.39 (0.82-2.35) |
| High intensity | 1.09 (0.59-2.01) |
| **Sex** | |
| **Women (n = 3156)** | |
| Moderate intensity | 1.03 (0.62-1.72) |
| High intensity | 1.27 (0.71-2.06) |
| **Men (n = 1968)** | |
| Moderate intensity | 1.64 (1.12-2.42) |
| High intensity | 1.36 (0.89-2.07) |
| **Fall in past year** | |
| **No (n = 4621)** | |
| Moderate intensity | 1.24 (0.89-1.73) |
| High intensity | 1.10 (0.76-1.59) |
| **Yes (n = 503)** | |
| Moderate intensity | 2.17 (0.98-4.80) |
| High intensity | 2.31 (1.01-5.29) |

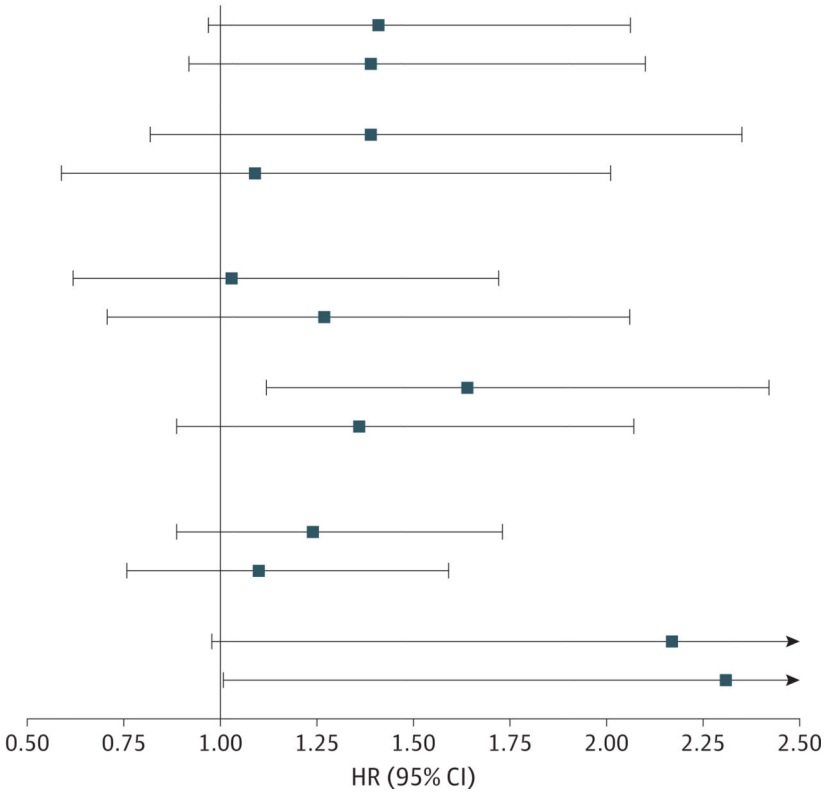


**Figure. Serious Fall Injury Events Among Relevant Subgroups According to Antihypertensive Intensity in Older Adults With Hypertension**

Hazard ratios (HR) were estimated using a subdistribution proportional hazards regression model for competing risk analyses. The reference group was the group using no antihypertensive medications. Follow-up was continued for up to 3 years. Antihypertensive intensity is defined in the Methods section. The propensity score–adjusted hazard ratios were adjusted for year of study entry, propensity score as a continuous variable, age, sex, fall injury in past year, use of an assistive device, difficulty walking, obesity, osteoporosis, Parkinson disease, depression, cognitive impairment, severe vision impairment, physical function score, prior myocardial infarction, prior stroke, heart failure, diabetes, psychosis, statin use, number of nonantihypertensive medications, self-perceived health, and blood pressure measured within the past 6 months. Dots represent point estimates for HRs, the width of the horizontal lines represents the 95% CIs, and arrows indicate that the upper limits of 95% CIs exceed 2.50.

**Table 1**

Baseline Characteristics by Antihypertensive Medication Intensity

| Characteristic[a] | Participants by Antihypertensive Medication Intensity, No. (%)[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Full Cohort (n = 4961) | | | | PS-Matched Cohort (n = 2849) | | | |
| | None (n = 697) | Moderate (n = 2711) | High (n = 1553) | *P* Value (PS-Adjusted *P*Value) | None (n = 662) | Moderate (n = 1455) | High (n = 732) | Standardized Difference, d1 (d2)[c] |
| Age, mean (SD), y | 80.1 (5.9) | 80.4 (5.8) | 79.8 (5.6) | .04 (.71) | 80.1 (5.9) | 80.4 (5.8) | 80.2 (5.6) | .072 (.057) |
| Female sex | 385 (55.2) | 1657 (61.1) | 1008 (64.9) | <.001 (.88) | 370 (55.9) | 848 (58.3) | 444 (60.7) | .046 (.074) |
| Nonwhite race | 66 (9.5) | 284 (10.5) | 228 (14.7) | <.001 (.40) | 61 (9.2) | 118 (8.1) | 90 (12.3) | .034 (.080) |
| Hispanic ethnicity | 42 (6.0) | 128 (4.7) | 71 (4.6) | .23 (.80) | 39 (5.9) | 72 (4.9) | 36 (4.9) | .031 (.027) |
| Educational level less than high school | 463 (66.4) | 1871 (69.0) | 1080 (69.5) | .21 (.80) | 437 (66.0) | 1024 (70.4) | 478 (65.3) | .096 (.038) |
| Perceived health less than very good | 353 (50.6) | 1577 (58.2) | 995 (64.1) | <.001 (.43) | 338 (51.1) | 764 (52.5) | 401 (54.8) | .034 (.055) |
| Current smoker | 60 (8.6) | 186 (6.9) | 86 (5.5) | .007 (.82) | 53 (8.0) | 111 (7.6) | 47 (6.4) | .018 (.044) |
| Body mass index ≥30[d] | 88 (12.6) | 514 (19.0) | 425 (27.4) | <.001 (.11) | 86 (13.0) | 195 (13.4) | 140 (19.1) | .011 (.113) |
| Prescription drug insurance | 517 (74.2) | 1883 (69.5) | 1100 (70.8) | .42 (.86) | 491 (74.2) | 1035 (71.1) | 528 (72.1) | .070 (.020) |
| Blood pressure measured within 6 mo | 651 (93.4) | 2552 (94.1) | 1493 (96.1) | .002 (.95) | 621 (93.8) | 1351 (92.9) | 691 (94.4) | .058 (.009) |
| Dependent in any BADLs | 237 (34.0) | 1040 (38.4) | 642 (41.3) | .001 (.46) | 224 (33.8) | 503 (34.6) | 241 (32.9) | .055 (.010) |
| Dependent in any IADLs | 355 (50.9) | 1516 (55.9) | 920 (59.2) | <.001 (.48) | 338 (51.1) | 744 (51.1) | 384 (52.5) | .020 (.009) |
| Mobility difficulty | 308 (44.2) | 1326 (48.9) | 839 (54.0) | <.001 (.39) | 292 (44.1) | 644 (44.3) | 319 (43.6) | .019 (.016) |
| Health limits social activities | 258 (37.0) | 999 (36.8) | 593 (38.2) | .45 (.55) | 239 (36.1) | 512 (35.2) | 240 (32.8) | .021 (.028) |
| Urinary incontinence | 112 (16.1) | 514 (19.0) | 313 (20.2) | .04 (.61) | 108 (16.3) | 256 (17.6) | 118 (16.1) | .029 (.001) |
| Cognitive impairment | 153 (22.0) | 495 (18.3) | 224 (14.4) | <.001 (.76) | 136 (20.5) | 233 (16.0) | 87 (11.9) | .021 (.143) |
| Depression | 128 (18.4) | 447 (16.5) | 238 (15.3) | .08 (.86) | 113 (17.1) | 221 (15.2) | 103 (14.1) | .011 (.048) |
| Fall injury in past year | 67 (9.6) | 273 (10.1) | 128 (8.2) | .12 (.97) | 60 (9.1) | 141 (9.7) | 59 (8.1) | .011 (.009) |
| Uses assistive device | 117 (16.8) | 558 (20.6) | 346 (22.3) | .006 (.48) | 111 (16.8) | 277 (19.0) | 124 (16.9) | .086 (.002) |
| Osteoporosis | 188 (27.0) | 661 (24.4) | 338 (21.8) | .005 (.79) | 178 (26.9) | 379 (26.0) | 187 (25.5) | .011 (.012) |
| Prior MI | 12 (1.7) | 65 (2.4) | 31 (2.0) | .97 (.91) | 12 (1.8) | 32 (2.2) | 11 (1.5) | .020 (.010) |

*JAMA Intern Med*. Author manuscript; available in PMC 2014 August 18.

| Characteristic[a] | Participants by Antihypertensive Medication Intensity, No. (%)[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Full Cohort (n = 4961) | | | | PS-Matched Cohort (n = 2849) | | | |
| | None (n = 697) | Moderate (n = 2711) | High (n = 1553) | *P* Value (PS-Adjusted *P*Value) | None (n = 662) | Moderate (n = 1455) | High (n = 732) | Standardized Difference, d1 (d2)[c] |
| Heart failure | 150 (21.5) | 754 (27.8) | 532 (34.3) | <.001 (.25) | 147 (22.2) | 329 (22.6) | 173 (23.6) | .011 (.011) |
| Diabetes | 215 (30.8) | 923 (34.0) | 698 (44.9) | <.001 (.24) | 208 (31.4) | 402 (27.6) | 245 (33.5) | .095 (.001) |
| Diabetes (complicated) | 71 (10.2) | 342 (12.6) | 274 (17.6) | <.001 (.30) | 69 (10.4) | 134 (9.2) | 91 (12.4) | .053 (.053) |
| Prior stroke | 101 (14.5) | 410 (15.1) | 265 (17.1) | .06 (.84) | 98 (14.8) | 202 (13.9) | 102 (13.9) | .019 (.034) |
| Cardiac arrhythmia | 250 (35.9) | 1108 (40.9) | 630 (40.6) | .14 (.71) | 231 (34.9) | 565 (38.8) | 266 (36.3) | .073 (.024) |
| Valvular disease | 181 (26.0) | 771 (28.4) | 483 (31.1) | .009 (.70) | 169 (25.5) | 371 (25.5) | 201 (27.5) | .021 (.015) |
| Atrial fibrillation | 126 (18.1) | 604 (22.3) | 372 (24.0) | .005 (.72) | 118 (17.8) | 294 (20.2) | 133 (18.2) | .037 (.003) |
| ESRD | 73 (10.5) | 405 (14.9) | 300 (19.3) | <.001 (.21) | 71 (10.7) | 183 (12.6) | 98 (13.4) | .077 (.079) |
| Blood loss anemia | 33 (4.7) | 133 (4.9) | 68 (4.4) | .55 (.84) | 27 (4.1) | 67 (4.6) | 29 (4.0) | .017 (.001) |
| Weight loss | 97 (13.9) | 307 (11.3) | 127 (8.2) | <.001 (.39) | 79 (11.9) | 167 (11.5) | 66 (9.0) | .034 (.061) |
| PVD | 206 (29.6) | 847 (31.2) | 487 (31.4) | .50 (.84) | 194 (29.3) | 436 (30.0) | 212 (29.0) | .025 (.002) |
| Psychosis | 44 (6.3) | 127 (4.7) | 62 (4.0) | .03 (.92) | 39 (5.9) | 58 (4.0) | 29 (4.0) | .078 (.074) |
| Elixhauser comorbidity score ≥3 | 461 (66.1) | 1827 (67.4) | 1084 (69.8) | .051 (.32) | 428 (64.7) | 926 (63.6) | 475 (64.9) | .017 (.033) |
| Statin use | 234 (33.6) | 1153 (42.5) | 755 (48.6) | <.001 (.54) | 225 (34.0) | 508 (34.9) | 281 (38.4) | .008 (.074) |
| Medications other than antihypertensives, mean (SD), No. | 5.6 (4.2) | 6.0 (4.4) | 6.8 (4.9) | <.001 (.28) | 5.4 (3.7) | 5.2 (3.6) | 5.5 (3.7) | .021 (.016) |

Abbreviations: BADLs, basic activities of daily living; d1, standardized difference between moderate-intensity and no-antihypertensive groups; d2, standardized difference between high-intensity and no-antihypertensive groups; ESRD, end-stage renal disease; IADLs, instrumental activities of daily living; MI, myocardial infarction; PS, propensity score; PVD, peripheral vascular disease.

[a] All variables were included in the PS-matched model.

[b] Participants include members of the 2004–2007 Medicare Current Beneficiary Survey cohort with hypertension. Antihypertensive medication intensity is defined in the Methods section. Data represent number (percentage) of participants unless otherwise indicated.

[c] Standardized differences compare mean differences between the comparison groups in units of the pooled SDs of the comparison groups, with values of less than 0.10 denoting negligible imbalance; see the Statistical Analysis subsection of the Methods section for details. In the full cohort before matching, the d1 and/or d2 was more than 0.10 for 25 ofthe 36PS covariates compared with 2 of 36 covariates for the matched subcohort.

[d] Body mass index was calculated as weight in kilograms divided by height in meters squared.

## Table 2

Effect of Antihypertensive Medication Use on the Occurrence of Serious Fall Injuries in Older Adults With Hypertension

| Antihypertensive Use | Adjusted Hazard Ratio (95% CI) | |
|---|---|---|
| | Full Cohort (n = 4961)[a] | PS-Matched Subcohort (n = 2849)[b] |
| Antihypertensive intensity[c] | | |
| None | 1 [Reference] | 1 [Reference] |
| Moderate | 1.40 (1.03–1.90) | 1.22 (0.80–1.71) |
| High | 1.28 (0.91–1.80) | 1.24 (0.83–1.84) |
| Antihypertensive class[d] | | |
| RAS blocker | 0.93 (0.76–1.14) | 1.06 (0.81–1.39) |
| β-Blocker | 0.96 (0.79–1.17) | 0.89 (0.66–1.20) |
| Calcium channel blocker | 1.06 (0.87–1.30) | 1.10 (0.83–1.45) |
| Diuretic | 1.06 (0.86–1.32) | 0.94 (0.70–1.26) |

Abbreviations: PS, propensity score; RAS, renin-angiotensin system.

[a] Based on competing risk model. In the full cohort, the adjusted hazard ratios accounted for PS as a continuous variable and for the following covariates: year of study entry, age, sex, fall injury in past year, use of assistive device, difficulty walking, obesity, osteoporosis, Parkinson disease, depression, cognitive impairment, severe vision impairment, physical function score, prior myocardial infarction, prior stroke, heart failure, diabetes, psychosis, statin use, number of nonantihypertensive medications, self-perceived health, and blood pressure measured within the past 6 months. The variables included in the PS are listed in Table 1.

[b] For the PS-matched subcohort analyses, the model included the same covariates except the PS, which was used to define the matched sets as a clustering factor.

[c] Moderate antihypertensive intensity was defined as 0.2 to 2.5 and high antihypertensive intensity as more than 2.5 of the defined daily dose of antihypertensive medications; those receiving less than 0.2 of the defined daily dose were included in the no-antihypertensive group. See the Methods section for details.

[d] Participants may use >1 class. The model hazard ratio contrasts users and nonusers (reference) for each antihypertensive medication class, adjusting for use of other antihypertensive classes.