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Greater Daily Defined Dose of Antihypertensive Medication Increases the Risk of Falls in Older People—A Population-Based Study

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Running heading: Daily defined dose antihypertensives and falls

ABSTRACT

OBJECTIVES: To determine whether there is a relationship between daily defined dose (DDD) of antihypertensive drugs and the risk of falls.

DESIGN: Prospective population-based cohort study.

SETTING: Tasmanian Study of Cognition and Gait, Australia.

PARTICIPANTS: Participants aged 60 to 86 randomly selected from the electoral roll.

MEASUREMENTS: Antihypertensive dose was quantified by estimating DDD, allowing standardized comparison of dosage between drug classes. Falls were identified prospectively over 12 months. The relative risk (RR) of falls associated with DDD was estimated using log

binomial regression adjusting for age, sex, body mass index, education, cardiovascular history, and other risk factors for falls.

RESULTS: Participants (N=409)had a mean age of 72.0±6.9, and 56% were male. Mean baseline blood pressure was 142/80 mmHg, and 54% were taking antihypertensive medications. One hundred sixty-one participants (39%) fell over the 12 months. Those who fell were on a higher DDD of antihypertensives (1.51±2.16 than those who did not (1.03±1.42) (p=.007). Higher DDD was independently associated with greater fall risk (RR=1.07, 95% confidence interval (CI)=1.02–1.11; p=.004), with a 48% greater risk in those with a DDD of more than 3 (RR=1.48, 95% CI=1.06–2.08; p=.02), particularly in those with a history of stroke (p for interaction .01). This effect remained even after excluding those not taking antihypertensives or stratifying according to presence of hypertension and medication use.

CONCLUSION: Higher dose of antihypertensive medication is independently associated with falls in older people, particularly in those with a history of previous stroke, and with more than 3 standard units conferring the highest risk.

Key words: falls, antihypertensive medication, older people

More than 30% of older people living in the community fall each year.[1] Falls can lead to injuries, such as hip fractures, that have significant social, economic and health costs.[2] Interactions between biological and environmental factors often cause such falls. The total number of medications taken has been linked to the risk of falls,[3] possibly because of age-related pharmacokinetic and pharmacodynamic changes [4] that create greater susceptibility to side effects and impaired cognition or gait. Antihypertensive drugs are among the most common types of medications that older people take, although the evidence linking antihypertensive medications to fall risk is inconsistent, with some studies reporting no

effect,[5–8] some a protective effect [9, 10] and others a greater risk of falls.[10–15] Study design may account for some of this inconsistency, such as retrospective falls ascertainment,[7, 8, 12, 13] inclusion of only hospitalized individuals, [6] or inadequate adjustment for potential confounders.[7, 13] In addition, many studies grouped different classes of antihypertensive medications into one category and hence may have missed subtle differences in effect of each class.

There are no prospective data on the association between dosage of antihypertensive therapy and falls, with previous studies treating drug use only as a binary variable. This is important, because a dose-response effect would assist in attributing causality to the relationship and in clarifying whether the observed association was different between classes of antihypertensive medications. Standardized comparison of dosage between drug classes can be estimated using the daily defined dose (DDD).[16] The aim of this population-based study was to investigate the association between exact quantification of antihypertensive medications (DDD) and the risk of prospectively ascertained falls. The hypotheses were that there would be a positive dose-response relationship between DDD and the risk of falls and that biological measures of fall risk would mediate or modify this relationship.

METHODS

Study population

The sample consisted of participants recruited into the Tasmanian Study of Cognition and Gait (TASCOG), conducted in Tasmania, Australia. Eligible participants were aged 60 to 85 and were randomly selected using age- and sex-stratified sampling from the southern Tasmanian electoral roll, a comprehensive list of residents. Because TASCOG was primarily aimed at examining the effects of brain aging on gait and cognition, people were excluded if they lived in residential care, had a history of dementia or Parkinson's disease, or had any contraindications to magnetic resonance imaging. Baseline measurements were taken

between January 2005 and December 2008. The Southern Tasmanian Health and Medical Human Research Ethics Committee approved this study (H7947). Informed consent was obtained from all participants.

Study variables

Medications and DDD quantification

A research nurse recorded prescription drug name, class, dose, and frequency during a face-to-face interview using a standardized form and participant prescriptions. A trained research assistant determined exact dose quantification of all antihypertensive medications using the World Health Organization Collaborating Center for Drug Statistics Methodology DDD system.[16] The DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults."[16] This system enables standardized comparison of antihypertensive drug usage between drug classes (e.g. 1×DDD = 75 mg atenolol or 2 mg trandolapril; 2 × DDD = 75 mg atenolol taken twice per day). Drugs were divided into the following main classes: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, and others used for cardiac disease (e.g., antiadrenergic agents (e.g., prazosin) and vasodilators (e.g., isosorbide mononitrate)). Additional analyses were performed with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers grouped as one category of renin angiotensin system medications. Combination drugs were separated into individual classes (e.g., Mono-plus was separated into the respective DDDs for fosinopril and hydrochlorothiazide).

Falls were defined according to the internationally agreed consensus definition of "an unexpected event in which the participant comes to rest on the ground, floor or lower level" [17] and recorded prospectively over 12 months using a falls calendar to aid memory. Participants were sent a questionnaire every 2 months after baseline to record information

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about falls that was then sent back to the research team in a postage-paid envelope. Failure to return a questionnaire triggered a follow-up reminder telephone call.

Baseline measurements

A physiotherapist measured gait speed (cm/s) at baseline using the 4.6-m GAITRite mat (CIR Systems, Havertown, PA) at usual walking pace. The average of six walks was used.

Cognitive function was measured using the Victoria Stroop color time test [18] as a measure of set-shifting and executive function, the Digit Symbol coding subtest of the Wechsler Adult Intelligence Scale-III as a measure of processing speed,[19] and the delayed recall subtest of the Hopkins Verbal Learning Test—Revised as a measure of memory.[20] These standardised tests were chosen because of the established relationships between executive function, memory, and processing speed and falls.[21]

The Physiological Profile Assessment (PPA) was used to measure sensorimotor factors affecting falls risk. The components are postural sway (on a foam mat with eyes open), knee extension strength, proprioception, visual edge contrast sensitivity, and simple reaction time. A weighting of these factors calculates a fall risk z-score that can correctly classify multiple and nonmultiple fallers with up to 75% accuracy.[22]

Quality of life was measured using the Australian Quality of Life standardized questionnaire.[23]

Other variables

Height and weight were measured, as was blood pressure after at least 5 minutes of rest using a standard protocol with two measures 30 seconds apart. Participants were classified as taking a psychotropic medication if they were taking an antidepressant, antipsychotic, sedative–hypnotic, antiepileptic, anti-Parkinson's medication, or narcotic. A standardized questionnaire was used to obtain information about medical history (falls in the previous 12 months; if told by a doctor they had a diagnosis of diabetes mellitus, stroke, angina pectoris,

acute myocardial infarction, and high cholesterol; smoking—regular smoker defined as using 7 cigarettes, cigars, or pipes every week for at least 3 months).

Statistical analysis

Participants were classified as fallers (any fall in the 12-month follow-up period) or nonfallers. A generalized linear model with a Poisson distribution and log-link function was used to estimate the association between total DDD and falls in three sequential models to estimate relative risk (RR): Model 1 (adjusting for age, sex, education), Model 2 (additionally adjusting for cardiovascular risk factors: body mass index (BMI), systolic and diastolic blood pressure, history of diabetes mellitus, stroke, angina pectoris, acute myocardial infarction, high cholesterol, or being a past smoker)), and Model 3 (further adjusting for other biological fall risk factors (PPA z-score, cognitive function, gait speed, psychotropic medication use and previous falls). Mediation was tested by comparing the β coefficient of DDD in the model with and without the biological factors. Missing values for falls risk factors were few (gait speed, n=9; PPA z-score, n=1; Stroop color time, n=9; digit symbol coding, n=5; Hopkins delayed recall, n=4; psychotropic medications, n=2) and imputed based on regression and the respective beta (β) coefficient of the variables age and sex. Interactions between DDD and other covariates (age, sex, cardiovascular risk factors, PPA z-score, cognitive tests, gait speed, psychotropic medication use) were assessed by including the product of those covariates in the regression. The same process was repeated for different classes of antihypertensive medications. The DDD variable was also divided into three categories (0, 1–3, >3) to more clearly quantify associations. Two secondary analyses were performed to explore confounding by indication. In the first analysis, participants not taking antihypertensive medication were divided into not hypertensive and hypertensive groups based on systolic blood pressure of less than 140 mmHg and 140 mmHg or more, respectively. The second analysis was performed excluding those not taking antihypertensive

medications. Analyses were performed using STATA version 12.1 (Stata Corp., College Station, TX).

RESULTS

Of the 804 eligible persons in the sample, 426 agreed to participate in this study, a response rate of 53%. Responders were younger (p=.01) and had a lower self-reported history of hypertension (p=.03) than nonresponders. Of the responders, 95.3% (n=406/426) completed at least five falls questionnaires. Participants were excluded from analyses if they did not return any falls questionnaires (n=6) or completed fewer than five falls questionnaires without reporting a fall (n=11). Of the baseline sample, 39.3% (161/409) reported a fall in the 12-month follow-up period, and 54.3% (222/409) were taking an antihypertensive medication. Five participants had missing drug dosage data, leaving404 participants (Supplementary Figure 1). Participants with missing drug dosage data had significantly lower Digit Symbol Coding test scores than those included (p=.03). Table 1 provides baseline characteristics for the overall sample, categorized into the three categories of DDD. After adjustment for age, sex, education, and cardiovascular risk factors, greater DDD was associated with quality of life (p<.001) but not gait speed (p=.29), cognitive function (Stroop Color Time p=.89, Digit Symbol Coding p=.33, Hopkins Delayed Recall p=.79), or PPA z-score (p=.92)~~both p>.05~~).

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Antihypertensive medication and the risk of falls

When used as a continuous variable, greater DDD of antihypertensive medication was associated with greater risk of falls after adjustment for age, sex, and education (Table 2: Model 1, RR=1.07, 95% CI=1.02–1.19; p=.004). This association remained after further adjustment for cardiovascular risk factors (Model 2, RR=1.07, 95% CI=1.02–1.12; p=.003) and other biological risk factors for falls (Model 3, RR=1.07, 95% CI=1.02–1.11; p=.004). Adjusting for previous falls made no difference to the results and was therefore not included

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in the model. There was an interaction between DDD and history of stroke (p for interaction .01), with stronger associations in those with a history of stroke (RR=1.36, 95% CI=1.14–1.61; p=.001) than those without a stroke (RR=1.05, 95% CI=1.00–1.10; p=.05). When DDD was divided into categories based on 0 (no antihypertensive medications), 1 to 3, or more than 3, those with a DDD of more than 3 had a 48% greater risk of falls than those not taking any antihypertensive medication (Model 3, RR=1.48, 95% CI=1.06–2.08; p=.02), but there was no statistically significant interaction with a history of stroke (p=.15). None of the biological factors mediated the relationship between DDD and falls. In secondary analyses, the risk of falls remained high in those with a DDD of more than 3 (Table 2; RR=1.64, 95% CI=1.10–2.45; p=.02, relative to individuals with hypertension not taking medication) or after excluding those not taking antihypertensives completely from the analysis (Table 2, RR=1.56, 95% CI=1.02–2.38; p=.04, relative to a DDD < 1).The binary variable "taking any antihypertensive (Yes/No)" was not associated with greater risk of falls (p=.26).

Antihypertensive class and risk of falls

After adjustment for age, sex, education, and cardiovascular factors (Table 3), none of the classes of medications (DDD or binary term) were associated with risk of falls (all p>.05).

DISCUSSION

A greater DDD of antihypertensive medication was independently associated with a greater risk of future falls, largely in those taking a DDD of more than 3, and particularly in those with a history of stroke. In contrast, a binary question regarding antihypertensive use was not associated with falls, indicating that DDD may be a more-sensitive measure.

This study has several strengths. It is the first prospective study to investigate the effect of antihypertensive DDD on the risk of falls. The population-based sample ensures more generalizability than clinical or volunteer samples. Rigorous methods were used for recording medication dose and falls, and the follow-up rate was high, although information was not

available on duration of drug use, changes during the follow-up period, or adherence, which may be important when accurately estimating associations.[14] Other falls risk factors and history of vascular disease were carefully adjusted for, although it is possible that some participants were on less antihypertensive medication because they were at higher fall risk, and this could be a source of confounding. It cannot be excluded that a higher DDD is a reflection of more-severe vascular disease (an indication for blood pressure treatment and also a falls-risk factor). The secondary analyses indicated that the greater risk of falls remained in those taking a DDD of more than 3 after accounting for confounding by indication, although it cannot be completely excluded that the identified relationships may be due to the presence of confounding factors such as subclinical vascular disease and other unmeasured comorbidities. These people may be frailer and therefore more likely to fall. Even so, the results suggests that a DDD of greater than 3 is a sensitive marker of risk of falls.

Although previous studies have reported that a greater DDD of antidepressants or numbers of medications overall [24, 25] increases the risk of falls, this is the first study reporting this for antihypertensives. The results suggest that the DDD of antihypertensive medication is a more-sensitive measure of fall risk than a simple question of usage. There is uncertainty whether certain classes of drugs have a greater risk of falls. When a previous meta-analysis[26] was updated,[3] it was found that antihypertensive agents, including diuretics, but not beta-blockers, were associated with falls in older people. Since then, angiotensin system antagonist use[9] and duration of prescription of thiazide diuretics and beta-blockers[10, 14] have been found to be associated with greater risk of falls. In the current study, although there was a trend toward greater risk of falls for all classes except “other” (comprising antiadrenergic agents and vasodilators), none reached statistical significance, probably reflecting limited power, although the finding of a relationship between DDD and falls suggests that dose of

antihypertensive medication is equally, if not more, important than drug class in determining fall risk.

A stronger association between DDD and falls risk was found in those with a history of stroke. Falls risk is higher after stroke than in the general population[27] because of cognitive and motor sequelae that may interact with antihypertensive drug dosage. Alternatively, a greater DDD in such people may be a surrogate marker of vascular burden and frailty, which lead to greater falls risk. Although participants with stroke had poorer physiological and cognitive function (results not shown), the interaction persisted after adjusting for these variables. Antihypertensive medication may also cause symptoms of dizziness and fatigue or promote orthostatic hypotension, but it was not possible to measure these.

These findings have clinical and research implications. From a clinical perspective, it is important to be mindful of the dose of antihypertensive medications prescribed to older people irrespective of drug class. Some older people may be taking more antihypertensive medication than necessary (particularly if there is a white coat effect),[28] creating an opportunity to intervene to reduce their risk of falls. The need for appropriate cardiovascular risk prevention should counterbalance this. Reduction in antihypertensive medication appears feasible and can reduce falls risk in older people who had previously fallen,[29] so the risk and preventative strategies for falls should be discussed with patients when commencing or increasing antihypertensive therapy.[30]

CONCLUSION

The DDD of antihypertensive medication was associated with greater risk of future falls. Future studies in this field should consider using DDD rather than a simple binary question of drug use.

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Author Contributions: Callisaya: data analysis, writing the manuscript. Sharman: research hypothesis, data interpretation, manuscript revision. Close, Lord: research hypothesis, manuscript revision. Srikanth: study concept, data and design of the Tasmanian Study of Cognition and Gait, research hypothesis, data interpretation, manuscript revision. All authors approved the final version of the submitted manuscript.

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REFERENCES

1. Callisaya ML, Blizzard L, Schmidt MD et al. Gait, gait variability and the risk of multiple incident falls in older people: A population-based study. Age Ageing 2011;40:481–487.

2. Campbell AJ, Borrie MJ, Spears GF et al. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. Age Ageing 1990;19:136–141.

3. 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;169:1952–1960.

4. Campbell AJ. Drug treatment as a cause of falls in old age. A review of the offending agents. Drugs Aging 1991;1:289–302.

5. Chu LW, Chi I, Chiu AY. Incidence and predictors of falls in the chinese elderly. Ann Acad Med Singapore 2005;34:60–72.

6. Frels C, Williams P, Narayanan S et al. Iatrogenic causes of falls in hospitalised elderly patients: A case-control study. Postgrad Med J 2002;78:487–489.

7. Gerdhem P, Ringsberg KA, Akesson K, et al. Clinical history and biologic age predicted falls better than objective functional tests. J Clin Epidemiol 2005;58:226–232.

8. Lee JS, Kwok T, Leung PC et al. Medical illnesses are more important than medications as risk factors of falls in older community dwellers? A cross-sectional study. Age Ageing 2006;35:246–251.

9. Wong AK, Lord SR, Sturnieks DL et al. Angiotensin system-blocking medications are associated with fewer falls over 12 months in community-dwelling older people. J Am Geriatr Soc 2013;61:776–781.

10. Gribbin J, Hubbard R, Gladman J et al. Risk of falls associated with antihypertensive medication: Self-controlled case series. Pharmacoepidemiol Drug Saf 2011;20:879–884.

11. Bergland A, Wyller TB. Risk factors for serious fall related injury in elderly women living at home. Inj Prev 2004;10:308–313.

12. Rozenfeld S, Camacho LA, Veras P. Medication as a risk factor for falls in older women in Brazil. Rev Panam Salud Publica 2003;13:369–375.

13. Tromp AM, Smit JH, Deeg DJ et al. Predictors for falls and fractures in the Longitudinal Aging Study Amsterdam. J Bone Miner Res 1998;13:1932–1939.

14. Butt DA, Mamdani M, Austin PC et al. The risk of falls on initiation of antihypertensive drugs in the elderly. Osteoporos Int 2013;24:2649–2657.

15. Butt DA, Mamdani M, Austin PC et al. The risk of hip fracture after initiating antihypertensive drugs in the elderly. Arch Intern Med 2012;172:1739–1744.

16. WHO Collaborating Centre for Drug Statistics Methodology. Daily Defined Dose: Definition and General Considerations [online]. Available at http://www.whocc.no/ddd/definition_and_general_considera/ Accessed March 16, 2013.

17. Lamb SE, Jorstad-Stein EC, Hauer K et al. Development of a common outcome data set for fall injury prevention trials: The Prevention of Falls Network Europe consensus. J Am Geriatr Soc 2005;53:1618–1622.

18. Spreen O, Strauss E. A Compendium of Neuropsychological Tests. Administration, Norms, and Commentary, 2nd Ed. New York: Oxford University Press, 1998.

19. Wechsler D. Wechsler Adult Intelligence Scale. New York, NY: Psychological Corporation, 1997.

20. Lezak M. Neuropsychological Assessment, 3rd ed. New York: Oxford University Press, 1995.

21. Martin KL, Blizzard L, Srikanth VK et al. Cognitive function modifies the effect of physiological function on the risk of multiple falls—a population-based study. J Gerontol A Biol Sci Med Sci 2013;68A:1091–1097

22. Lord SR, Menz HB, Tiedemann A. A physiological profile approach to falls risk assessment and prevention. Phys Ther 2003;83:237–252.

23. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: A psychometric measure of health-related quality of life. Qual Life Res 1999;8:209–224.

24. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. J Gerontol 1989;44:M112–M117.

25. Cumming RG, Miller JP, Kelsey JL et al. Medications and multiple falls in elderly people: The St. Louis OASIS study. Age Ageing 1991;20:455–461.

26. 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;47:40–50.

27. Batchelor FA, Mackintosh SF, Said CM et al. Falls after stroke. Int J Stroke 2012;7:482–490.

28. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281–1357.

29. van der Velde N, Stricker BH, Pols HA et al. Risk of falls after withdrawal of fall-risk-increasing drugs: A prospective cohort study. Br J Clin Pharmacol 2007;63:232–237.

30. Tinetti ME, McAvay GJ, Fried TR et al. Health outcome priorities among competing cardiovascular, fall injury, and medication-related symptom outcomes. J Am Geriatr Soc 2008;56:1409–1416.

Table 1 Characteristics of Study Participants

Characteristic	Total sample, n=409	Defined Daily Dose		
		0, n=187	1–3, n=167	>3, n=50
Age, mean±SD[c]	72.0±6.9	70.6±6.7	73.3±7.0[e]	72.7±6.4
Male, n (%)[b]	228 (55.8)	103 (55.1)	87 (52.1)	33 (66.0)
Body mass index, kg/m^2, mean±SD	27.9±4.6	26.9±4.2	28.5±4.9[e]	29.4±4.6[e]
Systolic blood pressure, mmHg, mean±SD	142.8±21.4	142.6±21.9	144.8±21.3	136.3±19.2
Diastolic blood pressure, mmHg, mean±SD	80.4±11.9	81.9±11.6	80.1±12.0	75.6±11.1[e]
Stroop color time, seconds, mean±SD	39.1±22.0	37.7±23.3	39.9±21.1	42.1±18.5
Digit symbol coding, mean±SD	49.8±15.1	51.2±15.3	50.0±14.9	45.2±12.6[e]
Hopkins delayed recall, mean±SD	7.5±3.0	7.8±2.9	7.4±3.3	7.4±2.9
Gait speed, cm/s, mean±SD [b]	113.3±22.5	116.5±21.4	111.1±22.0	107.0±24.5[f]
PP Physiological Profile Assessment z-score, mean±SD [b]	–0.25±0.85	–0.31±0.91	–0.21±0.81	–0.21±0.75
Quality of life, mean±SD [a]	23.2±5.2	20.7±4.1	24.9±5.0[d]	27.3±5.2[d]
Medical history, n(%)				
Diabetes mellitus	55 (13.5)	11 (5.9)	27 (16.2)[f]	17 (34.0)[e]
Stroke	36 (8.8)	9 (4.8)	20 (12.0)	7 (14.0)
Smoking history	207 (50.6)	92 (49.2)	78 (46.7)	35 (70.0)
Hypertension	205 (50.1)	20 (10.7)	138 (82.6)[d]	45 (90.0)[d]
Acute myocardial infarct	57 (13.9)	10 (5.4)	30 (18.0)[e]	16 (32.0)[d]
High cholesterol	178 (43.5)	59 (31.6)	83 (49.7)[e]	34 (68.0)[d]
Previous fall in past 12 months	68 (16.9)	31 (16.6)	26 (15.7)	12 (21.8)
Medication use				
Psychotropic, n (%)[c]	80 (19.7)	28 (15.0)	38 (22.8)	14 (28.0)
Antihypertensive, n (%)	222 (54.3)			
DDD, mean ±SD[b] (n=404)	1.22±1.76			
Type of antihypertensive, n (%)				
Angiotensin-converting enzyme inhibitor	95 (23.2)			
Angiotensin II receptor blocker	69 (16.9)			
Renin angiotensin system antagonist	161 (39.36)			
Beta-blocker	61 (14.9)			
Calcium channel blockers	63 (15.4)			
Diuretic	94 (23.0)			
Other	21 (5.1)			

SD=standard deviation.

Difference between nonfallers and any fallers: P<[a].001; [b].01; [c].05.

Differences between first defined daily dose (DDD) category and second or third category:

P<[d].001; [e].01; [f].05.

Table 2. Association Between Antihypertensive Medication and Falls

Antihypertensive Medication	No Falls	Any Fall			
			Model 1	Model 2	Model 3
	n (%)		Relative Risk (95% Confidence Interval)		
Taking any antihypertensive medication (n=409)	127 (57.2)	95 (42.8)	1.15 (0.90–1.48)	1.12 (0.87–1.44)	1.16 (0.89–1.51)
DDD (continuous) (n=404)			1.07 (1.02–1.18)[b]	1.07 (1.02–1.12)[b]	1.07 (1.02–1.11)[b]
DDD (category)					
0	121 (64.7)	66 (35.3)	1.00	1.00	1.00
1–3	100 (60.0)	67 (40.0)	1.06 (0.81–1.39)	1.03 (0.78–1.36)	1.02 (0.77–1.34)
>3	23 (46.0)	27 (54.0)	1.53 (1.11–2.11)[b]	1.50 (1.07–2.11)[c]	1.48 (1.06–2.08)[c]
DDD (category) secondary analysis[d]					
No antihypertensive medication and SBP ≥ 140 mmHg	65 (65.0)	35 (35.0)	1.00	1.00	1.00
No antihypertensive medication and SBP < 140 mmHg	56 (64.4)	31 (35.6)	1.05 (0.72–1.54)	1.21 (0.78–1.87)	1.24 (0.80–1.93)
1–3	100 (60.0)	67 (40.0)	1.09 (0.79–1.50)	1.11 (0.80–1.54)	1.11 (0.80–1.55)
>3	23 (46.0)	27 (54.0)	1.56 (1.08–2.25)[c]	1.64 (1.10–2.43)[c]	1.64 (1.10–2.45)[c]
DDD (category) secondary analysis[e]					
≤ 1	38 (64.4)	21 (35.6)	1.00	1.00	1.00
>1–3	62 (57.4)	46 42.6)	1.09 (0.72–1.65)	1.10 (0.73–1.66)	1.17 (0.77–1.77)
>3	23 46.0	27 (54.0)	1.48 (0.96–2.28)	1.49 (0.96–2.30)	1.56 (1.02,2.38)[c]

P<[a].001, [b].01, [c].05.

Model 1: adjusted for age, sex, education; Model 2: additional adjustment for cardiovascular risk factors; Model 3: additional adjustment for central nervous system active medication, gait speed, cognitive function tests, and Physiological Performance Assessment Z score; n=404 for defined daily dose (DDD) continuous and category analyses.

[d]Those not taking antihypertensive medication stratified according to presence (systolic blood pressure (SBP)>140mmHg) or absence (SBP<140mmHg) of hypertension.

[e]Excluding all participants not taking antihypertensive therapy.

Table 3. Association Between Type of Antihypertensive Medication and Falls (n=404)

Medication Type (Defined Daily Dose/d)	Model 1	Model 2
	Relative Risk (95% Confidence Interval)	
Angiotensin converting enzyme inhibitor	1.09 (0.96–1.24)	1.07 (0.94–1.23)
Angiotensin II receptor blocker	1.10 (0.93–1.31)	1.08 (0.90–1.28)
Renin angiotensin system	1.12 (0.99–1.25)	1.10 (0.97–1.24)
Beta-blocker	1.26 (0.87–1.83)	1.22 (0.83–1.80)
Calcium channel blocker	1.20 (0.99–1.44)	1.20 (0.99–1.45)
Diuretic	1.12 (0.96–1.29)	1.11 (0.96–1.28)
Other	0.94 (0.62–1.41)	0.90 (0.59–1.38)

Model 1: adjusted for age, sex, education; Model 2: additional adjustment for cardiovascular risk factors.

Figure 1. Derivation of sample.