令和８年度
東北医科薬科大学 大学院 医学研究科
医学専攻博士課程
一般・社会人入学試験（一次募集）
【基礎学力試験　問題用紙】

注意事項

１．解答用紙に問題番号を記載すること。

２．試験中に問題冊子の印刷不鮮明、ページの落丁・乱丁および解答用紙の汚れ等に気づいた場合は、手を挙げて知らせること。

３．不正行為に対しては厳正に対処します。

４．試験終了後、問題冊子は回収します。

受験番号：	氏　名：

1

プライマリ・ケア機能を発揮する総合診療医の能力について近接性・包括性・協調性・継続性・責任性（ACCCA モデル）の観点から述べて下さい。記述の際、ご自身の経験から地域で活躍する総合診療医に求められるスキルについても触れて下さい。

2

以下の問題 1. または問題 2 のどちらかを選び、答えてください。

1. 心不全の治療薬を適宜分類し、それぞれについて簡潔に説明を加えてください。
2. 治験における第 I 相から第 IV 相について簡潔に説明を加えてください。また、治験に関与する組織・職種について簡潔に説明してください。

3

以下の問題について 2 問とも答えよ。

1. 19 歳の大学 1 年生が、過去 3 か月にわたり被害関係妄想や命令性の幻聴を呈しており、両親に付き添われてあなたの外来を初診で受診した。服薬を拒否している場合、この患者に対して、どのような対応・治療が考えられるか。倫理的配慮も含めて述べよ。

2. 高齢者が身体疾患を主訴に来院したが、うつ状態である場合、どのような鑑別・検査・治療が必要かを述べよ。

4

以下の問題について 2 問とも答えよ。

1．インスリン以外の糖尿病治療薬を適宜分類し、それぞれについて主な作用（薬理機序）と臨床的な特徴などを述べよ。
2．糖尿病患者を診療するにあたり、まずは血糖コントロール目標を定める必要がある。　65 歳未満の一般成人と 65 歳以上の高齢者に分けて、血糖コントロール目標の設定について述べよ。

5

以下のいずれか１つの問題を選択して答えよ。

１．慢性腎不全における腎代替療法について述べよ。

２．腎血管性高血圧の病態・診断・治療について述べよ。

6

添付の論文 Dave et al. JAMA internal medicine. 2024;184:661 について以下の問題につき 2問とも解答せよ。本文とそれに対する Invited Commentary の両方を参考に解答せよ。

1）この論文の要旨とあなたが考えるその臨床的意義についてまとめよ（字数制限無）。

2）この論文で用いられている target trial emulation とはどのような手法か。本文、Invited Commentary の記載を参考に解答せよ（字数制限無）。

【問題６の論文】

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Antihypertensive Medication and Fracture Risk in Older Veterans Health Administration Nursing Home Residents

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IMPORTANCE Limited evidence exists on the association between initiation of antihypertensive medication and risk of fractures in older long-term nursing home residents.

OBJECTIVE To assess the association between antihypertensive medication initiation and risk of fracture.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective cohort study using target trial emulation for data derived from 29 648 older long-term care nursing home residents in the Veterans Health Administration (VA) from January 1, 2006, to October 31, 2019. Data were analyzed from December 1, 2021, to November 11, 2023.

EXPOSURE Episodes of antihypertensive medication initiation were identified, and eligible initiation episodes were matched with comparable controls who did not initiate therapy.

MAIN OUTCOME AND MEASURES The primary outcome was nontraumatic fracture of the humerus, hip, pelvis, radius, or ulna within 30 days of antihypertensive medication initiation. Results were computed among subgroups of residents with dementia, across systolic and diastolic blood pressure thresholds of 140 and 80 mm Hg, respectively, and with use of prior antihypertensive therapies. Analyses were adjusted for more than 50 baseline covariates using 1:4 propensity score matching.

RESULTS Data from 29 648 individuals were included in this study (mean [SD] age, 78.0 [8.4] years; 28 952 [97.7%] male). In the propensity score–matched cohort of 64 710 residents (mean [SD] age, 77.9 [8.5] years), the incidence rate of fractures per 100 person-years in residents initiating antihypertensive medication was 5.4 compared with 2.2 in the control arm. This finding corresponded to an adjusted hazard ratio (HR) of 2.42 (95% CI, 1.43-4.08) and an adjusted excess risk per 100 person-years of 3.12 (95% CI, 0.95-6.78). Antihypertensive medication initiation was also associated with higher risk of severe falls requiring hospitalizations or emergency department visits (HR, 1.80 [95% CI, 1.53-2.13]) and syncope (HR, 1.69 [95% CI, 1.30-2.19]). The magnitude of fracture risk was numerically higher among subgroups of residents with dementia (HR, 3.28 [95% CI, 1.76-6.10]), systolic blood pressure of 140 mm Hg or higher (HR, 3.12 [95% CI, 1.71-5.69]), diastolic blood pressure of 80 mm Hg or higher (HR, 4.41 [95% CI, 1.67-11.68]), and no recent antihypertensive medication use (HR, 4.77 [95% CI, 1.49-15.32]).

CONCLUSIONS AND RELEVANCE Findings indicated that initiation of antihypertensive medication was associated with elevated risks of fractures and falls. These risks were numerically higher among residents with dementia, higher baseline blood pressures values, and no recent antihypertensive medication use. Caution and additional monitoring are advised when initiating antihypertensive medication in this vulnerable population.

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Multimedia

Supplemental content

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Unintentional injuries are the fifth leading cause of mortality among older adults, and falls are responsible for two-thirds of such injuries.[1] Long-term care residents are a highly vulnerable population characterized by substantial multimorbidity, polypharmacy, and frailty, and the majority will experience a fall in any given year.[2,3] More than a quarter of those falls will lead to a serious injury, and between 10% and 15% will result in fractures, hospitalizations, or death.[4,5]

Prescription medications represent a leading modifiable risk factor for falls.[6] Given that the prevalence of diagnosed hypertension among older adults exceeds 70%,[7] blood pressure–lowering therapies are the most frequently used medications in this age group. However, orthostatic hypotension—the putative trigger for many falls, and consequently, fractures—is a frequent complication, and the immediate period after treatment initiation is associated with the greatest risk.[8,9] Older adults in nursing homes are especially predisposed to falls due to the age-related physiological alterations that compromise the adaptive response to postural changes (eg, venous pooling, decreased cardiac output, and decreased baroreceptor sensitivity),[10,11] as well as a higher prevalence of risk factors associated with falls and fractures, including osteoporosis, limited mobility, and cognitive impairment.[12-14] Taken together, these findings suggest that frail older nursing home residents are more likely to experience a fall and with each fall are more likely to experience fractures.

Currently, there is a paucity of evidence examining the association between antihypertensive therapy initiation and risk of fractures among older nursing home residents, as prior clinical trial and observational data have been derived from community-dwelling patients.[15-18] Further, the clinical utility of prior observational studies is constrained by the lack of information on blood pressure values, which can render the causal estimates subject to residual confounding. Moreover, these studies cannot provide insights into how fracture risks differ across blood pressure thresholds, despite some earlier evidence suggesting a higher risk of orthostasis in individuals with elevated blood pressure.[19] Finally, while patients with dementia are at a higher risk of diagnosed hypertension and susceptibility to falls and fall-related injuries,[20] there is no prior evidence clarifying these risks in this vulnerable population.

Consequently, a new large-scale epidemiologic investigation that examines the risk of fracture associated with initiation of antihypertensive therapies in this population is needed. We used a target trial emulation approach in the national Veterans Health Administration (VA) nursing home data spanning from January 1, 2006, to October 31, 2019, to elucidate the risk of fracture, as well as severe falls, associated with antihypertensive medication initiation.

Key Points

Question Is initiating antihypertensive medication associated with increased fracture risk among older long-term Veterans Health Administration nursing home residents?

Findings In a 1:4 propensity score–matched cohort of 64 710 residents, initiation of antihypertensive medication was associated with increased fracture risk and adjusted excess risk per 100 person-years. This risk was numerically higher in subgroups of residents with dementia or with systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 80 mm Hg or higher.

Meaning Findings from this cohort study suggest that caution and additional monitoring are advised when initiating antihypertensive medication in this vulnerable population.

Methods

This cohort study received institutional review board approval from Stanford University, with a waiver of the requirement to obtain informed consent as it met the criteria of secondary research for which consent is not required. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Target Trial Emulation

Our target trial emulation framework had 2 steps.[21] First, we specified the protocol of a hypothetical pragmatic unblinded target trial that aimed to ascertain the risk of fracture associated with antihypertensive medication initiation among long-term VA nursing home residents. **Table 1** summarizes the key design elements of such a trial. In brief, the population of this target trial was older adults (≥65 years) receiving a stable blood pressure–lowering regimen who were subsequently randomly allocated to receive an additional blood pressure–lowering medication (exposure arm) or continue with their existing treatment (control arm). The primary outcome was fracture occurring within 30 days of treatment assignment. Second, we used a large database of nursing home residents within the VA to emulate this target trial. The design elements of our emulation approach are articulated in further detail below and summarized in Table 1.

Data Sources

Study participants were drawn from the VA Corporate Data Warehouse, a national repository of electronic health records from all VA facilities in the US. Data from January 1, 2006, to October 31, 2019, were used to identify nursing home residents, using previously validated approaches.[22] Medical records from nursing home stays were linked to other data sources, including acute hospital stays as well as outpatient and emergency department visits. Pertinent data elements of interest included sociodemographic characteristics as well as inpatient and outpatient encounters. Bar code medication administration data were used to capture medications administered in the nursing home. Information on systolic and diastolic blood pressure values were obtained using the vital status files. Finally, the Minimum Data Set from the Centers for Medicare & Medicaid Services was linked to provide information on activities of daily living and cognitive functioning.

Eligibility Criteria and Treatment Strategies

Treatment initiation was defined as an increase in the number of blood pressure–lowering medication classes compared

with the prior 4 weeks (ie, therapy augmentation), and instances of switching were thus implicitly excluded. Patients initiating their first antihypertensive medication (ie, not receiving any prior treatment in the preceding 4 weeks) were also included. The date of medication initiation was designated as the index date for the exposure group.

Cohort membership required patients to be at least 65 years of age, have no evidence of end-stage kidney disease (ESKD) in the preceding year, and have at least 1 documented measurement of systolic and diastolic blood pressure within 2 weeks of the index date. In instances of multiple blood pressure assessments, the most recent value prior to the index date was used.

Patients were also required to maintain a stable antihypertensive treatment regimen for 4 consecutive weeks prior to the index date (ie, date of medication initiation), defined as no changes in the number of antihypertensive drug classes in each of the preceding 4 weeks. To exclude short-term stays (eg, acute rehabilitation) and allow for adequate washout of antihypertensive therapies, the study cohort was restricted to patients with at least 90 days of nursing home stay. Medication use was assessed using bar code medication administration data starting from the 91st day.

For patients in the control group, a synthetic index date was assigned using the following approach. Each week of the nursing home stay was assessed for being a potential control week by evaluating whether the eligibility criteria were met (ie, stable regimen, documented blood pressure, and no ESKD). Such an approach allowed for the creation of a suitable control group that adhered to the same eligibility as the exposure group. Patients were allowed to contribute multiple treatment or control episodes as long as the eligibility criteria were met.

Table 1. Specification and Emulation of a Target Trial Evaluating Initiation of Antihypertensive Medication and Risk of Severe Falls

Protocol component	Target trial specification	Target trial emulation using VA data
Eligibility criteria	1 Age ≥65 y between 2006 and 2019 2 Residence in a long-term care nursing home in the VA 3 Receiving a stable antihypertensive therapy regimen 4 No evidence of end-stage kidney disease	Criteria 1, 2, and 4 were the same as the target trial. For criterion 3, patients were required to have a stable antihypertensive medication regimen for 4 wk and not have used the initiated therapy in the 28-d washout period prior to initiation.
Treatment strategies	Exposure arm: addition of antihypertensive class to existing regimen; control arm: continuation of existing regimen	Treatment strategies were the same as the target trial. Medication use was ascertained using BCMA data.
Treatment assignment	Individuals were randomly assigned to 1 of the 2 treatment strategies; neither the patient nor prescriber was blinded to the intervention	Patients were evaluated weekly for eligibility and were classified into 1 of 2 treatment strategies. Randomization was emulated by adjusting for imbalances in >50 baseline covariates using a 1:4 propensity score–matching approach. Neither the patient nor prescriber was blinded to the intervention.
Follow-up	Starts on the day after the eligibility criteria are fulfilled and ends on the 30th day	Same as the target trial
Outcomes	Fracture	Same as the target trial
Causal contrasts	Per-protocol effect	Same as the target trial
Statistical analysis	IR of fractures per 100 person-years; HR for fractures using control arm as the referent category	Adjusted IRs and relative risks were estimated via 1:4 propensity score matching

Abbreviations: BCMA, bar-coded medication administration; IR, incidence rate; HR, hazard ratio; VA, Veterans Health Administration.

Treatment Assignment

To emulate the randomization procedure in the target trial, we accounted and adjusted for imbalances in patient characteristics across the 2 groups using a propensity score (PS)–matching approach, which used logistic regressions to model the probability of initiating an antihypertensive medication, using more than 50 baseline covariates that are described in **Table 2.** All covariates were assessed 365 days prior to the index date except for blood pressure values and the baseline antihypertensive regimen (eg, number of antihypertensive drug classes), which were evaluated within 2 and 4 weeks prior to the index date, respectively. Other covariates were also assessed, including patient demographics (eg, age, race, year, or week since community living center admission), indication for antihypertensive medication use and other cardiovascular conditions (eg, diabetes, chronic kidney disease, or atrial fibrillation), cardiovascular medications (eg, statins), cognitive and physical function, and other factors associated with risk of falls and fractures (eg, history of falls, use of sedative hypnotics). Self-reported race was assessed to further characterize the cohort; categories included Black, White, other (including Asian/Pacific Islander, American Indian, and multiple race), and missing.

Follow-Up and Outcomes

Patients began contributing follow-up time from the index date until discharge from the nursing home, discontinuation of index medication for the exposure group, initiation of a new antihypertensive medication in the control group, end of the study period, the occurrence of the outcome, a maximum of 30 days, or end of the study date (October 31, 2019). We chose a 30-day time frame, aligning with the anticipated high-risk period in which orthostasis and subsequently fracture risk are expected to manifest most acutely; however, other longer time horizons were also considered as sensitivity analyses.

The primary outcome was a composite of nontraumatic pelvic fracture; surgically treated hip fracture; and fractures of the humerus, radius, or ulna requiring intervention within 30 days of the index date (eTable 1 in Supplement 1). In instances when 2 criteria were required (eg, hip fracture and surgery), the date of the second event was designated as the outcome date. These algorithms have been previously validated and have positive predictive values exceeding 92%.[23,24]

Statistical Analysis

Given the larger number of potential controls compared with treated patients, 1:4 PS matching was implemented using a nearest-neighbor approach. The performance of the PS model in adjusting for differences in baseline characteristics was assessed by cross-tabulating baseline characteristics prior to and after matching. Incidence rates for the outcomes (per 100

Table 2. Baseline Characteristics Prior to and After 1:4 PS Matching

Sociodemographic characteristic	Treatment initiation or control episodes, No. (%)					
	Prior to PS matching			1:4 PS matching		
	Treatment (n = 12 942)	Control (n = 610 217)	Std diff[a]	Treatment (n = 12 942)	Control (n = 51 768)	Std diff[a]
Age, mean (SD), y	78.2 (8.4)	78.8 (8.4)	7.6	78.2 (8.4)	78.2 (8.4)	0.6
Sex						
Male	12 640 (97.7)	596 089 (97.7)	0.1	12 640 (97.7)	50 528 (97.6)	0.4
Female	302 (2.3)	14 128 (2.3)	0.1	302 (2.3)	1240 (2.4)	0.2
Race						
Black	2498 (19.3)	108 467 (17.8)	3.9	2498 (19.3)	10 075 (19.5)	0.4
White	9286 (71.8)	443 253 (72.6)	2.0	9286 (71.8)	37 001 (71.5)	0.6
Other[b]	326 (2.5)	14 520 (2.4)	0.9	326 (2.5)	1251 (2.4)	0.7
Missing	832 (6.4)	43 977 (7.2)	3.1	832 (6.4)	3441 (6.6)	0.9
Week of nursing home admission, mean (SD)	38.9 (24.7)	43.7 (25.1)	19.3	38.9 (24.7)	39.3 (23.4)	1.7
Medication class initiated						
ACE inhibitor	2657 (20.5)	NA	NA	2657 (20.5)	NA	NA
ARB	425 (3.3)	NA	NA	425 (3.3)	NA	NA
β-Blocker	2138 (16.5)	NA	NA	2138 (16.5)	NA	NA
α-Blocker	260 (2.0)	NA	NA	260 (2.0)	NA	NA
Loop diuretic	3636 (28.1)	NA	NA	3636 (28.1)	NA	NA
Thiazide diuretic	1574 (12.2)	NA	NA	1574 (12.2)	NA	NA
DHP-CCB	1800 (13.9)	NA	NA	1800 (13.9)	NA	NA
Non-DHP-CCB	302 (2.3)	NA	NA	302 (2.3)	NA	NA
Aldosterone antagonist	644 (5.0)	NA	NA	644 (5.0)	NA	NA
Baseline medication use						
ACE inhibitor	4751 (36.7)	242 493 (39.7)	6.3	4751 (36.7)	20 052 (38.7)	4.2
ARB	1168 (9.0)	56 676 (9.3)	0.9	1168 (9.0)	4926 (9.5)	1.7
β-Blocker	7626 (58.9)	401 550 (65.8)	14.2	7626 (58.9)	31 055 (60.0)	2.2
α-Blocker	464 (3.6)	13 812 (2.3)	7.9	464 (3.6)	2030 (3.9)	1.8
Loop diuretic	4775 (36.9)	206 193 (33.8)	6.5	4775 (36.9)	20 013 (38.7)	3.6
Thiazide diuretic	1593 (12.3)	69 593 (11.4)	2.8	1593 (12.3)	7063 (13.6)	4.0
DHP-CCB	3462 (26.8)	177 317 (29.1)	5.1	3462 (26.8)	14 577 (28.2)	3.2
Non-DHP-CCB	770 (5.9)	37 221 (6.1)	0.6	770 (5.9)	3338 (6.4)	2.1
Aldosterone antagonist	931 (7.2)	33 366 (5.5)	7.1	931 (7.2)	3977 (7.7)	1.9
No. of HTN medications, mean (SD)	1.24 (1.03)	1.87 (0.94)	63.9	1.24 (1.03)	1.31 (0.76)	7.7
Cardiometabolic factors						
Type 2 diabetes	7249 (56.0)	322 521 (52.9)	6.3	7249 (56.0)	29 276 (56.6)	1.1
SBP (most recent), mean (SD), mm Hg	136.3 (23.1)	130.2 (19.3)	28.5	136.3 (23.1)	136.4 (20.9)	0.5
DBP (most recent), mean (SD), mm Hg	72.5 (12.1)	70.4 (10.7)	18.5	72.5 (12.2)	72.5 (11.2)	0.6
Stroke	5350 (41.3)	253 884 (41.6)	0.5	5350 (41.3)	21 418 (41.4)	0.1
Myocardial infarction	1998 (15.4)	74 608 (12.2)	9.3	1998 (15.4)	7565 (14.6)	2.3
Heart failure	6227 (48.1)	242 030 (39.7)	17.1	6227 (48.1)	25 701 (49.6)	3.1
Insulin	4617 (35.7)	190 905 (31.3)	9.3	4617 (35.7)	17 553 (33.9)	3.7
Other medical condition						
Osteoarthritis	4267 (33.0)	193 682 (31.7)	2.6	4267 (33.0)	17 122 (33.1)	0.2
Osteoporosis or osteopenia	859 (6.6)	41 668 (6.8)	0.8	859 (6.6)	3417 (6.6)	0.1
Malignant neoplasm	3525 (27.2)	151 771 (24.9)	5.4	3525 (27.2)	13 938 (26.9)	0.7
Dementia	7213 (55.7)	380 672 (62.4)	13.6	7213 (55.7)	28 840 (55.7)	0.0
CFS score, mean (SD)	2.06 (0.83)	2.16 (0.85)	11.9	2.06 (0.83)	2.06 (0.82)	0.4
Activities of daily living score, mean (SD)	13.01 (7.46)	13.38 (7.58)	4.9	13.01 (7.46)	13.15 (7.52)	1.9
History of falls	8222 (63.5)	388 863 (63.7)	0.4	8222 (63.5)	33 055 (63.9)	0.7
Recent fall (<30 d)	3236 (25.0)	147 262 (24.1)	2.0	3236 (25.0)	12 838 (24.8)	0.5
History of fracture	892 (6.9)	36 914 (6.0)	3.4	892 (6.9)	3591 (6.9)	0.2
Carotid sinus hypersensitivity	10 (0.1)	224 (0.0)	1.7	10 (0.1)	50 (0.1)	0.7

(continued)

Table 2. Baseline Characteristics Prior to and After 1:4 PS Matching (continued)

Sociodemographic characteristic	Treatment initiation or control episodes, No. (%)					
	Prior to PS matching			1:4 PS matching		
	Treatment (n = 12 942)	Control (n = 610 217)	Std diff[a]	Treatment (n = 12 942)	Control (n = 51 768)	Std diff[a]
Non-CVD medications						
Opioid	6998 (54.1)	282 636 (46.3)	15.6	6998 (54.1)	28 263 (54.6)	1.1
Muscle relaxer	1673 (12.9)	66 860 (11.0)	6.1	1673 (12.9)	6640 (12.8)	0.3
Benzodiazepine	4429 (34.2)	180 821 (29.6)	9.9	4429 (34.2)	17 733 (34.3)	0.1
Sedative (eg, zolpidem)	1465 (11.3)	58 869 (9.6)	5.5	1465 (11.3)	5856 (11.3)	0.0

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CFS, cognitive function scale; CVD, cardiovascular disease; DBP, diastolic blood pressure; DHP-CCB, dihydropyridine calcium channel blocker; HTN, hypertension; NA, not applicable; PS, propensity score; SBP, systolic blood pressure; Std diff, standardized difference.

[a] Std diff greater than 10% indicates a meaningful difference in the patient characteristic; after 1:4 PS matching, there were no differences that exceeded this threshold.

[b] Other race includes Asian/Pacific Islander, American Indian, and multiple races.

person-years) and adjusted hazard ratios (HRs), along with their corresponding 95% CIs, were estimated using Cox proportional hazards regression models. Robust variance estimators were used to account for the same patient potentially contributing multiple episodes. The adjusted excess risk (ER) for the primary outcome was estimated by $I_O \times (HR - 1)$, where I_O is the rate of the outcome in the control group per 100-person years, and HR is the adjusted HR (95% CI calculated analogously). Given the short time horizon over which study outcomes were assessed (30 days), we did not consider time-varying specifications of PS or censoring weights.

Several additional analyses were conducted to assess the robustness of the study findings. First, we varied specifications pertaining to exposure-related censoring and maximum length of follow-up. Specifically, in addition to the per-protocol analysis, in which we censored patients at the time of treatment discontinuation (or initiation for the control group), we carried the index exposure forward to mimic an intention-to-treat (ITT) approach. For the as-treated analysis, we varied the duration of follow-up from 30 days to 45, 60, and 90 days after initiation. Second, a sensitivity analysis extending the washout period from 4 to 12 weeks was conducted. Third, in light of the high number of initiations of loop diuretics in our cohort (28.1% of initiations), we conducted an analysis excluding patients who initiated loop diuretics to investigate whether this drug class had a disproportionate association with the outcome. Fourth, we examined other fall-related outcomes, including falls requiring emergency department visits or hospitalizations and occurrence of syncope. We also expanded the primary outcome to include traumatic brain injury hospitalizations and other less frequently occurring fractures affecting the rib, sternum, thoracic, and lumbar regions (eTable 1 in Supplement 1). Fifth, we adjusted for the following 3 facility-level quality measures in the PS models: unannounced survey ratings, patient-to-staff ratings, and quality star ratings. For this analysis, the cohort was restricted from 2016 to coincide with the introduction of quality ratings for VA nursing homes.[25] Sixth, we assessed for the presence of effect modification among patients with dementia, systolic blood pressure (<140, ≥140 mm Hg) and diastolic blood pressure (<80, ≥80 mm Hg), age (<80, ≥80 years), and baseline use of antihypertensive medication (0, >0). For all subgroup analyses, the PSs were re-estimated and the cohorts were rematched.

Analyses were conducted from December 1, 2021, to November 11, 2023, using SAS software, version 8.3 (SAS Institute Inc). Statistical significance was defined as a 95% CI excluding 1 for HR and excluding 0 for ER.

Results

Data from 29 648 older long-term residents were included in this study (mean [SD] age, 78.0 [8.4] years; 28 952 [97.7%] male and 696 [2.3%] female; and 5102 [17.2%] Black, 21 770 [73.4%] White, 717 [2.4%] categorized as having other race, and 2059 [6.9%] with missing race data). After the inclusion and exclusion criteria were applied, we identified 12 942 and 610 217 eligible treatment initiation episodes (eFigure in Supplement 1); after 1:4 matching, 12 942 initiation episodes were matched to 51 768 control episodes. Table 2 and eTable 2 in Supplement 1 give the distribution of baseline characteristics of the 2 groups prior to matching. Patients in the treatment and control groups differed with respect to pertinent baseline characteristics (defined as standardized difference >10%). For instance, patients initiating treatment had higher systolic and diastolic blood pressures values, were more likely to be diagnosed with heart failure and myocardial infarction, and had a greater likelihood of using opioids and benzodiazepines. After 1:4 PS matching, the baseline characteristics of the 64 710 PS-matched cohort (mean [SD] age, 77.9 [8.5] years), including systolic and diastolic blood pressure values, were well balanced in both groups, and no standardized difference exceeded 10%.

Primary Analysis

In the overall 1:4 PS-matched cohort, the incidence rate of fracture (per 100 person-years) in the antihypertensive arm was 5.4 compared with 2.2 in the control arm, during a mean (SD) follow-up of 18.2 (8.7) days for the antihypertensive group and 16.8 (8.7) days for the control group. This finding corresponded to an adjusted HR of 2.42 (95% CI, 1.43-4.08) cases of fractures per 100 person-years and an adjusted ER of 3.12 (95% CI, 0.95-6.78) cases of fractures per 100 person-years (**Table 3**).

Table 3. Risk of Fall-Related Events Among Nursing Home Residents Initiating Antihypertensive Medication

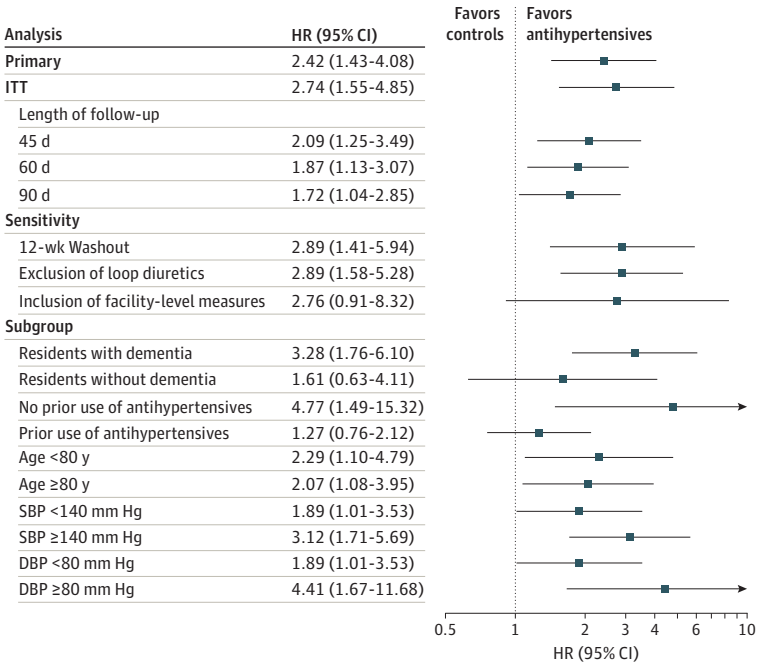
Event	Pooled analysis		
	No. of events (IR)[a]		
	Treated (n = 12 942)	Control (n = 51 768)	HR (95% CI)
Fracture[b]	46 (5.4)	56 (2.2)	2.42 (1.43-4.08)
Severe fall	246 (28.8)	386 (15.5)	1.80 (1.53-2.13)
Syncope	135 (15.8)	231 (9.3)	1.69 (1.30-2.19)
Expanded outcome definition[b]	52 (6.1)	66 (2.6)	2.30 (1.44-3.69)

Abbreviations: HR, hazard ratio; IR, incidence rate.

[a] Incidence rate per 100 person-years of follow-up. The mean (SD) follow-up in the treatment group was 18.2 (8.7) days and in the control arm was 16.8 (8.7) days.

[b] The primary outcome was a composite end point of nontraumatic pelvic fracture; surgically treated hip fracture; and fractures of the humerus, radius, or ulna requiring intervention. In the expanded outcome definition, this definition was expanded to encompass traumatic brain injury hospitalization and other less frequently occurring fractures affecting the rib, sternum, thoracic, and lumbar regions.

Figure. Adjusted Risk of Fracture Among Nursing Home Residents Initiating Antihypertensive Medication: Sensitivity and Subgroup Analyses



Analyses were adjusted using 1:4 propensity score matching for baseline covariates described in Table 2. For all subgroup analyses, the propensity scores were re-estimated and the cohorts were rematched. DBP indicates diastolic blood pressure; HR, hazard ratio; ITT, intention to treat, and SBP, systolic blood pressure.

Secondary Analysis

Findings were consistent for secondary end points (Table 3). Use of an antihypertensive medication was associated with an increase in risk of severe falls necessitating emergency department visits or hospitalizations (HR, 1.80 [95% CI, 1.53-2.13]; ER, 12.40 [95% CI, 8.22-17.52]), occurrence of syncope (HR, 1.69 [95% CI, 1.30-2.19]; ER, 6.42 [95% CI, 2.79-11.07]), and the expanded outcome definition, which encompassed traumatic brain injury hospitalizations and other fractures (HR, 2.30 [95% CI, 1.44-3.69]; ER, 3.38 [95% CI, 1.14-6.99]).

In the sensitivity analyses in which the length of follow-up was varied for the primary outcome of fracture, the magnitude of the HR values decreased stepwise from 2.42 (95% CI, 1.43-4.08) (30 days) to 1.72 (95% CI, 1.04-2.85) (90 days) (**Figure**). The results from other sensitivity analyses, including the ITT, exclusion of patients initiating loop diuretic medications, 12-week washout period, and inclusion of facility-level quality measures, were consistent with the primary findings.

Among patients without dementia, those with antihypertensive medication initiation had a numerically higher risk of fracture (HR, 1.61 [95% CI, 0.63-4.11]). By contrast, among patients with dementia, antihypertensive use was associated with higher risk of fracture (HR, 3.28 [95% CI, 1.76-6.10]; P = . 21 for heterogeneity for the outcome of fracture by dementia status). The risk of fracture did not vary across subgroups of age but was numerically higher among patients with systolic blood pressure of 140 mm Hg or higher (HR, 3.12 [95% CI, 1.71-5.69]) vs less than 140 mm Hg (HR, 1.89 [95% CI, 1.01-3.53]) (P = .26 for heterogeneity), and for patients with diastolic blood pressure of 80 mm Hg or higher (HR, 4.41 [95% CI, 1.67-11.68]) vs less than 80 mm Hg (HR, 1.89 [95% CI, 1.01-3.53]) (P = .15).

Finally, risk of fracture was numerically higher among patients with no antihypertensive medication use in the baseline period (HR, 4.77 [95% CI, 1.49-15.32]) compared with patients with this use (HR, 1.27 [95% CI, 0.76-2.12]) (P = .21).

Discussion

It has been postulated that initiating antihypertensive medication may increase the risk of fracture given the potential of these drugs to induce orthostasis; however, there is a paucity of data examining this association among long-term nursing home residents, who already have a higher baseline risk of such events.[10-14] Using data from the VA and a target trial emulation approach, this cohort study found that antihypertensive medication initiation was associated with increased risk of fracture. Findings were consistent across a range of secondary outcomes, including severe falls and syncope, and sensitivity analyses.

The findings of this study have important clinical implications. Despite ongoing efforts, the incidence of fall-related mortality has continued to trend upward in the United States, nearly doubling from 2000 to 2013, from 29.6 to 56.7 deaths per 100 000 adults.[26] Falls are also the primary contributor to fractures, which are associated with worsening global health and a pronounced increase in overall mortality. Notably, among older nursing home residents, hip fractures alone have been linked to 1-year mortality rates exceeding 40%.[27] When contextualized to this study, our observed excess rates of fracture per 100-person years due to antihypertensive medication initiation were high and ranged between 3.1 for the overall cohort and approaching 5.0 among certain vulnerable subgroups (eg, residents with dementia). Fracture prevention is crucial in this population from a clinical and public health perspective, and commonly prescribed medications, such as antihypertensive medications, represent a prominent modifiable risk factor. Nursing home facilities already implement high vigilance and preventive measures against falls and fractures[28]; however, despite these existing guardrails, patients initiating antihypertensive medication had a higher risk of fractures and falls.

Our study findings suggested a potential elevated risk of fracture associated with the initiation of antihypertensive medications in patients with dementia and in patients with elevated blood pressure. However, these interactions did not reach statistical significance and therefore could also be attributed to chance. Patients with dementia have a higher risk of falls and fractures due to a variety of factors, including impaired cognition, gait abnormalities, and use of other medications that are associated with fall risk (eg, benzodiazepines).[20,29] This risk could be further exacerbated in this subgroup during antihypertensive medication initiation due to poorer reporting of subjective symptoms associated with orthostasis and falls (eg, dizziness). The seemingly counterintuitive finding of a higher fracture risk in patients with elevated systolic and diastolic blood pressures may be explained by 2 factors. First, prior research suggests that orthostasis may be more prevalent among individuals with augmented blood pressures.[19,30] Additionally, secondary contributory factors, such as elevated vascular resistance or amplified autonomic dysfunction, are more prevalent in patients with hypertension, thereby undermining the standard physiological adaptions to postural changes.[31]

Although data on the risk of fractures due to antihypertensive use are lacking for older adults in long-term nursing home care among individuals with dementia and separately by systolic and diastolic blood pressure levels, prior investigations have examined these associations in community-dwelling older adults. For instance, a Canadian study using a self-controlled case series approach found a 43% increased risk of hip fractures within the first 45 days after initiating antihypertensive medication, which aligns with our study findings.[8] Other studies with longer time horizons and considering mechanisms relating to bone metabolism have reported a more attenuated or null association compared with our analysis.[32] Our findings are also more consistent with observational studies of community-dwelling adults that examined fall risk as an outcome during the immediate period following antihypertensive medication initiation.[33]

Nursing home residents present a unique clinical challenge, as they can often derive benefit from using antihypertensive medication to manage conditions such as heart failure that increase the risk of cardiovascular events[34] while simultaneously being predisposed to experiencing adverse reactions, such as falls and fractures, owing to factors such as frailty.[12-14] This study focused on clarifying 1 of the risks associated with antihypertensive use in this population. Clinically, factors guiding the choice of antihypertensive medication in older nursing home patients should include a comprehensive battery of factors that extend beyond just the risk of falls and fractures, such as the patient's complete medical history, specific clinical indication for treatment, and potential for adverse reactions, and should contextualize a limited life expectancy against the anticipated time horizon over which the cardiovascular benefits are likely to manifest.

Strengths and Limitations

This study has several strengths, including the use of a target trial emulation design with a large national database that comprehensively captures rich longitudinal patient-level clinical and functioning data. Additionally, we specifically accounted for baseline blood pressure values, a critical factor when comparing users and nonusers of antihypertensive medication. This distinction is important as prior cohort studies did not restrict analysis to patients with comparable blood pressure levels, potentially introducing confounding. Furthermore, information on medication administration, rather than on prescribing or dispensing data, were used, mitigating concerns for exposure misclassification. Finally, the study's focus on the escalation in antihypertensive treatment, rather than drug switching, captured changes in therapy that are more relevant to fracture and fall risk.

This study also has limitations. First, it is noteworthy that the demographic composition of VA nursing home patients is predominantly male, thereby constraining the generalizability of our findings to other nursing home populations. This

limitation is salient when considering the sex-specific variations in the incidence of particular fractures, such as hip fractures, which tend to be higher in women compared with men; however, men may face higher mortality rates when experiencing such events.[27,35] Second, the study lacked sufficient power to assess differences in the risk of fractures across different drug classes. Nonetheless, prior data suggest that the magnitude of such risk may not vary across drug classes, at least in the period immediately subsequent to drug initiation.[8] Third, as in all observational studies, we may have residual confounding. However, we took several steps to reduce the likelihood of confounding by assessing and adjusting for pertinent patient characteristics, such as blood pressure, using a PS matching approach, restricting our cohort to new users of study medications, and excluding potential confounders, such as ESKD. Finally, akin to prior studies examining risk of falls with antihypertensive medication use,[15-18] this investigation focuses on treatment initiation and did not consider dosage escalation, which represents another form of treatment intensification that could also be associated with fracture risk.

Conclusions

Findings from this cohort study suggest that, given the widespread use of antihypertensive medication in older adults, any observed association with fracture risk has significant implications for clinical medicine and public health. This study sheds light on the potential impact of fracture risk associated with antihypertensive medication use among long-term nursing home residents, emphasizing the need for caution when initiating therapy, especially in the high-risk period after drug initiation.

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Invited Commentary

Blood Pressure Management and Falls in Nursing Home Residents—A Matter of Balance

Muna Thalji Canales, MD, MS; Ronald I. Shorr, MD, MS

In this study, Dave et al[1] harness national Veterans Health Administration (VHA) clinical data to examine the association between initiation of a new antihypertensive agent with the incidence of fall-related fractures in residents at VHA nursing homes, or community living centers. In this carefully designed study, residents who received a new antihypertensive agent had more than 2-fold greater risk of fractures compared with those who did not (adjusted hazard ratio [aHR], 2.42 [95% CI, 1.43-4.08]). This practice was also associated with 1.8-fold greater risk of serious falls (HR, 1.80 [95% CI, 1.52-2.13]) and 1.7-fold greater risk of syncope (HR, 1.69 [95% CI, 1.30-2.19]). Subgroup analysis revealed an even higher risk of fractures in nursing home residents with dementia (HR, 3.28 [95% CI, 1.76-6.10]), elevated systolic (HR, 3.12 [95% CI, 1.71-5.69]) or diastolic (HR, 4.41 [95% CI, 1.67-11.68]) blood pressure, and those who had not used antihypertensives (HR, 4.77 [95% CI, 1.49-15.32]). These findings create a compelling narrative that rapidly decreasing blood pressure in nursing home residents may cause orthostatic hypotension, leading to falls and fractures. They also extend the findings from a smaller study of participants in the Systolic Blood Pressure Intervention Trial (SPRINT).[2] In a secondary analysis of SPRINT, participants randomized to intensive treatment of systolic hypertension (blood pressure <120 mm Hg) were more likely to experience hypotension, and possibly syncope, but not falls.[2]

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Dave et al[1] took several measures to optimize the internal validity of their observational study. First, they used a target trial emulation format that allows for more valid causal inference in observational studies by minimizing selection bias. Key measures taken to emulate a trial of new antihypertensive therapy include a requirement for a washout period of 4 weeks prior to initiation of therapy and presentation of both an intention-to-treat and per protocol analysis to assess veterans who did not continue in their allocated group of this retrospective study. Additional measures that strengthen validity of this study include the effective use of propensity matching to address confounding by indication for receipt of new antihypertensive therapy; residual confounding may exist but Dave et al[1] matched on 50 relevant variables and demonstrated balance between groups on all of these after matching. Ascertainment of the primary outcome was via comprehensive diagnosis and procedure codes that have been previously validated, and the 30-day time frame for follow-up is in line with a biologically plausible temporal connection between hypotension resulting from a new medication and the resulting event. Also, Dave et al[1] leveraged granular clinical data to obtain blood pressure, demographic, comorbidity, and medication data to answer their question. Finally, with such a large sample size of nursing home