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ORIGINAL PAPER

Blood pressure lowering medication initiation and fracture risk: a SWAN pharmacoepidemiology study

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Abstract

Summary We examined the fracture risk after initiation of blood pressure–lowering drugs compared with initiation of antidepressants. Multivariable regression models demonstrated an increased risk of fracture among women initiating a blood pressure–lowering medication (HR 1.73, 95% CI 1.02–2.95). This is likely related to an increased risk of falls.

Purpose Initiation of blood pressure–lowering drugs has been associated with fractures in several studies, presumably due to an increase in the risk of falls. However, these studies used self-controlled designs without active comparators. We examined the risk of fractures after initiation of blood pressure lowering drugs compared with initiation of antidepressants.

Methods Women participants in the Study of Women Across the Nation (SWAN) were potentially eligible if they initiated blood pressure–lowering or antidepressant drugs during follow-up. To reduce the risk of confounding, we estimated a propensity score that included potential confounders including age, menopausal status, osteoporosis, and osteoporosis medication use. The propensity score was used to match subjects in both groups and we then constructed multivariable logistic regression models comparing the risk of any fracture. Sensitivity analyses assessed a limited range of fractures less likely related to trauma.

Results Among the 3302 potentially eligible women participating in the SWAN cohort, we were able to propensity-score match 289 women who initiated a blood pressure–lowering medication with 289 who initiated an antidepressant. Multivariable logistic regression models demonstrated an increased risk of fracture among women initiating a blood pressure lowering medication (OR 1.74, 95% CI 1.02–2.95). After excluding fractures of the digits and face, the results were similar (OR 1.57, 95% CI 0.88–2.81).

Conclusions There was evidence of an increased risk in fractures among women initiating blood pressure–lowering medications compared to those initiating antidepressants. This is likely related to an increased risk of falling.

Keywords Antihypertensive drugs · Fractures · Epidemiology

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11657-019-0618-x) contains supplementary material, which is available to authorized users.

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Introduction

Prior literature suggests that initiation of antihypertensive drugs may be associated with fractures [1–3]. These studies have examined fracture risk in the immediate period after starting medications that lower blood pressure. Results suggest that starting such medications may be associated with an increased risk of fracture. The absolute risk of fracture in this population was not estimated in one large study but was noted to be quite small in another study [2]. As well, comparisons were not made to the fracture risk after initiating other drugs, a so-called active comparator design [4]. Prior drug safety studies have demonstrated that the period after drug initiation is often associated with adverse events. This provides the rationale for using active comparators (i.e., people starting a different medication).

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Low blood pressure can cause dizziness and fainting and several studies have described an increased risk of falls immediately after the start of certain blood pressure–lowering medications [5, 6]. One study that focused on loop diuretics found an increased risk of falls in the day after the start of drug, but the risk was not observed thereafter [7]. The absolute risk was very low: 1 excess fall for every 271 loop diuretic initiations. It is also possible that hypertension could be associated with a reduction in bone strength. Some literature supports this possibility but not all [8].

Obtaining better evidence on these issues will allow providers and patients to better estimate the risk-benefit tradeoff with initiating blood pressure–lowering drugs. These drugs have clear benefits in selected patients, with respect to reducing stroke and myocardial infarction risks [9–11]. Thus, we set out to study the risk of fracture associated with initiation of blood pressure–lowering medications.

Methods

Study design and sample The current study involved participants in the Study of Women Across the Nation (SWAN), which is a community-based, multi-ethnic longitudinal observational cohort study of the menopause transition. A detailed description of SWAN has been published previously [12]. Briefly, SWAN enrolled 3302 pre- or early peri-menopausal women in the USA at seven clinical sites. Women were between the ages of 42 and 52 years at enrollment. During follow-up, women are seen approximately every year to monitor a variety of measures, and data are analyzed by visit. Information on medication use is collected prospectively. Women are instructed to bring in all medication containers, and trained interviewers transcribe all preparations onto study forms. SWAN has collected information on participants every 1–2 years from 1997 to 2016.

The current study examined whether use of blood pressure lowering agents was associated with fractures. To address this question, two separate analyses were conducted. First, we compared the relative risk of fracture after initiation of a blood pressure–lowering medication to the risk after initiation of an antidepressant. While some data suggest a reduction in bone mineral density among patients taking antidepressants, the preponderance of data argues against any increased risk of fracture in this patient group [13]. Second, we compared the risk of fracture pre- and post-initiation of blood pressure–lowering medications. Thus, women who started a blood pressure–lowering medication were identified. Then, the risk of fracture was calculated in the year prior and the year after the start of a blood pressure–lowering agent. These rates were compared. These comparisons were repeated for the two and three years prior to and after the start of such medications.

From the SWAN cohort, several selection criteria were applied to both analyses. First, we identified new users of any blood pressure–lowering agent, including ACE inhibitors, alpha agonists, angiotensin receptor blockers, calcium channel blockers, beta blockers, non-thiazide diuretics, thiazide diuretics, and other agents. We allowed prevalent users of these agents in the eligible cohort, but only included women who started a new agent during follow-up. For the first analyses, we also identified new users of any antidepressant. We allowed prevalent users of antidepressants into the cohort, but the comparison group only included new users.

All study participants gave written informed consent. The study protocol was approved by each SWAN site's Institutional Review Boards.

Assessment of medication use At each visit, interviewers administered questionnaires to ascertain medication use since the last study visit. Use was verified by inspection of medication containers. If medication containers were not available, medication lists were reviewed. Medications were classified from generic or brand names using the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City). Blood pressure–lowering agents were assessed at each visit to determine initiation, but dosage of the agents was not available. We had relatively few women using each type of blood pressure–lowering drug, so these analyses treat the category as a group without sub-analyses by type.

Assessment of fractures At baseline, participants reported prior fractures since age 20. During follow-up annual visits, participants self-reported incident fractures, including the anatomic site and number of fractures since their last study visit. The reliability of self-reported fractures with medical records confirmation has been documented in several studies. In SWAN, a sample of self-reported fractures between was adjudicated; out of 193 self-reported fractures with medical records, there was a 96% (95% confidence interval, 92–98%) positive predictive value. Anatomic fracture sites used for the current analyses include the following: wrist, hip, spine, pelvis/sacrum, ribs, arm-above wrist, let, shoulder, ankle and patella, fingers, toes, and face. Two secondary fracture outcomes were defined for these analyses: (1) all of the above fractures, excluding fractures of the digits and face, and (2) only including fractures of the wrist, arm, hip, spine, and pelvis.

Fracture risk factors (covariates) The visit prior to entry into the study cohort was defined as a baseline. SWAN participants underwent measurement of height and weight for calculation of body mass index (BMI, weight in kilograms divided by the square of height in meters). Participants completed interviewer-administered or self-administered questionnaires that assessed demographic characteristics (age, race, ethnicity,

income, education, and marital status), lifestyle factors (alcohol intake and tobacco use), self-assessed health status, social support (items from the 20 item Medical Outcomes Study Social Support Survey), [14] vasomotor symptoms, and self-reported comorbid conditions (osteoporosis, any cancer, diabetes mellitus). Bone active medications were considered as covariates, such as bisphosphonates, hormone therapy, oral glucocorticoids, calcium, and vitamin D. In addition, physical activity was measured using a modified version of the Baecke Physical Activity Questionnaire (range 3–15) [15, 16]. Menopause transition stage was assessed in SWAN based on bleeding criteria. Categories were pre-menopause (no change in the predictability of menses during the last year), early or late peri-menopause (decreased predictability of menses but having with gaps of up to 11 months), and post-menopause (no menses for 12 or more months). Women without a clear date of menopause or who reported hysterectomy were classified as "unknown" menopausal status. Menopause transition stage was updated at every study visit. Once a woman had advanced to a later transition stage she could not be reclassified to an earlier transition stage.

Statistical analyses As noted, two different analyses were conducted. The primary analysis compared the fracture risk in women starting a blood pressure–lowering medication to those starting an antidepressant. To improve the balance between these two groups, we only included women who could be matched with women in the other cohort using a propensity score. A propensity score is the probability of use of an intervention compared with non-use [17]. Propensity score matching is a technique to address potential confounding by several factors with a reduced number of covariates (degrees of freedom) in the multivariable models [18, 19]. A greedy matching algorithm was used to find the best possible match and the matching caliper was set at 0.2 of the standard deviation of the logit of the PS [20]. The propensity score models included variables that were potential confounders (i.e., associated with both exposure and outcome); this included age, menopausal status, osteoporosis, and bisphosphonate use. We did not include variables in the propensity score logistic regression that were very strong predictors of one drug category or the other as these often create a strong imbalance in the propensity score distributions. Instead, we tested such variables in the multivariable models after creating the propensity score-matched cohorts.

The primary analyses examined the incidence rate and relative risk for any fracture, the primary outcome. We first calculated incidence rates (fractures per 1000 person-years) among the two drug exposure groups. Incidence rate ratios with 95% confidence intervals were estimated. We then examined the relative risk using discrete survival logistic regression models based on the type of fracture. The type of fractures was separated into three groups for analyses: (a) all fractures, (b) any fracture except fingers/toes/facial, and (c) only wrist, arm hips, spine, and pelvis.

Model 1 adjusted for age and race. All other variables mentioned above were entered one by one into Model 1, and those with p values ≤ 0.10 were then entered into Model 2. We also added in variables from the propensity score, including osteoporosis and bisphosphonate use. Model 3 was run in a subgroup of SWAN participants who had bone mineral density (BMD) measured. (BMD of the lumbar spine, femoral neck, and total hip (g/cm^2) was measured by dual-energy X-ray absorptiometry (DXA) using Hologic instruments (Hologic Inc., Waltham, MA). Model 3 included all covariates in Model 2 plus femoral neck BMD. Body mass index was also forced into Model 3.

All models of fractures of the wrist, arm, hips, spine, and pelvis classified race as white or non-white, as there were not enough women of other race/ethnicity to allow the models to converge. For ease in interpretation, the same covariates were used in all models. Lastly, we examined the incidence of fracture before and after the initiation of antihypertensive medications. All analyses are performed using SAS 9.3 (SAS, Cary NC).

Results

There were 298 women in SWAN who initiated antidepressants and 639 using blood pressure–lowering treatments. We were able to match 97% of the women in the antidepressant group. The participants of SWAN that were included had a mean age of 52 years and approximately three-quarters had more than a high school education (Table 1). About half were White and the other half were Black, Chinese, Japanese, or Hispanic. Almost half were current or past tobacco users and approximately three-quarters were peri- or post-menopausal. The median time women reported using antihypertensive medications was three years and two years for antidepressants.

We observed 29 fractures in the cohort of women initiating blood pressure–lowering treatments and 20 fractures among women initiating antidepressants (Table 2). The incidence rates were 33.22 (95% CI 22.24–47.74) fractures per 1000 person-years for women initiating blood pressure–lowering medications and 23.31 (95% CI 14.23–36.00) for those initiating antidepressants. The incidence rate ratio was 1.43 (95% CI 0.81–2.52).

We compared the risk of fracture among the women initiating blood pressure–lowering medications with those initiating antidepressants in logistic regression models. While the groups were matched on propensity score, we added additional adjustment in successive models (Table 3). After adjusting for age, race, and osteoporosis diagnosis, we found that women initiating blood pressure lowering–medications had a significantly increased risk of all types of fractures (OR 1.74,

Table 1 Baseline characteristics of women in the SWAN cohort initiating blood pressure–lowering drug or antidepressant drugs after propensity score matching

	Total $N = 578$	Blood pressure lowering user $N = 289$	Antidepressant user $N = 289$	Standardized mean difference
	N (%) or mean (± SD)			
Age, years	51.7 (± 4.7)	51.7 (± 4.6)	51.6 (± 4.7)	0.01
Spine BMD, g/cm2	1.04 (± 0.15)	1.06 (± 0.16)	1.03 (± 0.15)	0.22
Femoral neck BMD, g/cm2	0.81 (± 0.13)	0.82 (± 0.13)	0.81 (± 0.13)	0.12
BMI, kg/m2	28.7 (± 7.1)	30.6 (± 7.6)	26.8 (± 6.0)	0.56
CES-D	10.4 (± 9.9)	8.9 (± 9.4)	11.9 (± 10.3)	0.31
Physical activity	7.7 (±1.8)	7.6 (± 1.8)	7.8 (± 1.8)	0.13
Educational attainment				0.36
High school or less	126 (21.8)	84 (29.1)	42 (14.5)	
Post-high school	448 77.5)	204 (70.6)	244 (84.4)	
Tobacco use				0.17
Past or current	274 (47.4)	124 (42.9)	150 (51.9)	
SWAN site				
Michigan	89 (15.4)	53 (18.3)	36 (12.5)	0.16
Mass General	92 (15.9)	40 (13.8)	52 (18.0)	0.11
UC Davis	80 (13.8)	51 (17.6)	29 (10.0)	0.09
UCLA	81 (14.0)	36 (12.5)	45 (15.6)	0.13
Pittsburgh	92 (15.9)	39 (13.5)	53 (18.3)	0.19
Chicago	63 (10.9)	39 (13.5)	24 (8.3)	0.17
New Jersey	81 (14.0)	31 (10.7)	50 (17.3)	0.22
Race/ethnicity				
White	295 (51.0)	92 (31.8)	203 (70.2)	0.83
Black	162 (28.0)	117 (40.5)	45 (15.6)	0.56
Chinese	36 (6.2)	24 (8.3)	12 (4.2)	0.17
Japanese	41 (7.1)	26 (9.0)	15 (5.2)	0.15
Hispanic	44 (7.6)	30 (10.4)	14 (4.8)	0.21
Menopausal status				
Pre-menopausal	63 (10.9)	29 (10.0)	34 (11.8)	0.06
Peri-menopausal	248 (42.9)	123 (42.6)	125 (43.3)	0.01
Post-menopausal	194 (33.6)	101 (34.9)	93 (32.2)	0.06
Unknown menopause or s/p hysterectomy	73 (12.6)	36 (12.5)	37 (12.8)	0.01
Medication use				
Osteoporosis meds	10 (1.7)	4 (1.4)	6 (2.1)	0.07
SERM	87 (15.1)	42 (14.5)	45 (15.6)	0.03
Corticosteroids	29 (5.0)	13 (4.5)	16 (5.5)	0.05
Vitamin D supplements	259 (44.8)	131 (45.3)	128 (44.3)	0.01
Calcium supplements	313 (54.2)	157 (54.3)	156 (54.0)	0.02
Comorbid conditions				
Osteoporosis	19 (3.3)	9 (3.1)	10 (3.5)	0.02
Diabetes	36 (6.2)	32 (11.1)	4 (1.4)	0.41
Cancers	7 (1.2)	3 (1.0)	4 (1.4)	0.05
Alcohol intake				
None	272 (47.1)	155 (53.6)	117 (40.5)	0.29
Moderate	127 (22.0)	59 (20.4)	68 (23.5)	0.08
High	130 (22.5)	51 (17.6)	79 (27.3)	0.25
Fractures				
All fractures	19 (3.3)	9 (3.1)	10 (3.5)	0.21
Fractures, excluding fingers/toes/face	16 (2.8)	8 (2.8)	8 (2.8)	0.21
Wrist, arm, hip, spine, pelvis	7 (1.2)	2 (0.7)	5 (1.7)	0.21

BMI, body mass index; *BMD*, bone mineral density; *SERM*, selective estrogen receptor modulator; *CES-D*, Center for Epidemiologic Studies—Depression Scale, 20-item scale, with a range of 0–60. Propensity scores include age, menopausal status, osteoporosis, and osteoporosis medications

Table 2 Fracture incidence rates and rate ratios for propensity score-matched cohorts of drug initiators among women enrolled in SWAN

Fracture type	Blood pressure–lowering initiators			Antidepressant initiators			
	# fractures	Person-time	Incidence rate* (95% CI)	# fractures	Person-time	Incidence rate* (95% CI)	Incidence rate ratio (95% CI)**
All fractures	29	873	33.22 (22.24–47.74)	20	858	23.31 (14.23–36.00)	1.43 (0.81–2.52)
Exclude digit and face fractures	22	873	25.20 (15.79–38.15)	18	858	21.00 (12.43–33.16)	1.20 (0.64–2.24)
Include only the wrist, arm, hip, spine, and pelvic fractures	6	873	6.87 (2.51–14.96)	6	858	6.99 (2.55–15.22)	0.98 (0.32–3.05)

*Per thousand person-years

**Incidence rate ratio comparing blood pressure lowering initiators with antidepressant initiators (reference)

95% CI 1.02–2.95), as well as a numerically elevated (albeit statistically non-significant) risk for fractures excluding digit and facial fractures (OR 1.57, 95% CI 0.88–2.81). This effect was stronger among the sub-group of women who also had BMD information (Table 3; the full list of covariates and their parameter estimates is shown in Supplemental Table 1).

Because of the potential for unmeasured confounding across the two cohorts, we also performed an alternative analysis examining women's risk of fracture before and after initiating blood pressure–lowering medications (Table 4). The incidence rate ratios showed no increase (OR 0.96, 95% CI 0.29–3.16) when we looked at the period one visit before and one visit after initiation of blood pressure medications. As the period of observation was lengthened, the incidence rate ratio increased.

Discussion

All medications have potential benefits and harms. Blood pressure–lowering medications are effective for cardiovascular prevention and are among the most widely used drugs in middle age and older adults, but concerns have been raised about bone health and fracture risk. We examined the risk of fracture among women during a vulnerable time for bone health and found a suggestion of an increase in fracture risk compared with women initiating antidepressant medications.

The evidence is relatively strong that blood pressure–lowering medications are associated with a short-term risk of falls [5, 7]. Prior work has also found an increased risk of fractures among this population; however, the absolute risk of fracture was not estimated in all prior studies. We found an absolute fracture risk of 33.2 per 1000 person-years for these women with a mean age of 52 years in whom approximately three-quarters were peri- or post-menopausal. We would anticipate that the risk of fracture among women initiating blood pressure–lowering medications would continue to rise with increasing age. Although our sample size did not permit a subgroup analysis for specific types of fractures, the health risk of hip fractures is substantial and compares to the risk of cardiovascular events [21]. Thus, a small increase in the fracture risk after initiation of blood pressure–lowering medications should serve as a reminder to address fracture prevention.

The combined lifetime risk for the hip, forearm, and vertebral fractures coming to clinical attention is around 40%, equivalent to the risk for cardiovascular disease [22]. This risk needs to be balanced against the potential for cardiovascular benefit of blood pressure–lowering medications. Elevated blood pressure is a well-described risk factor for cardiovascular morbidity and mortality. Moreover, the use of blood pressure–lowering medications reduces the risk of cardiovascular events by 25–50%, depending on the underlying risk of the population [9–11]. The absolute risk reduction varies but is

Table 3 Probability of fracture among women matched on propensity score in SWAN initiating blood pressure–lowering medications compared with women initiating antidepressant medications

Fracture types	Model 1 ($N = 578$)	Model 2 ($N = 578$)	Model 3 ($N = 370$)
	Odds ratio (95% confidence interval)		
All fractures	1.68 (0.99–2.85)	1.74 (1.02–2.95)	1.64 (0.85–3.15)
Excludes digit and face fractures	1.52 (0.85–2.69)	1.57 (0.88–2.81)	1.33 (0.68–4.60)
Include only the wrist, arm, hip, spine, and pelvic fractures	0.90 (0.39 2.40)	0.95 (0.36–2.52)	1.10 (0.33–3.67)

Model 1 was adjusted for age and race. Model 2 was adjusted for age, race, and osteoporosis. Model 3 was run in participants with bone mineral density information and was adjusted for age, race (White and non-Whites), osteoporosis, and femoral neck bone mineral density and BMI

Table 4 Fracture incidence rates and rate ratios before and after initiation of antihypertensive drugs among women enrolled in SWAN

	Before initiation			After initiation			
	# fractures	Person-years	Incidence rate* (95% CI)	# fractures	Person-years	Incidence rate* (95% CI)	Incidence rate ratio (95% CI)
All fractures							
Before and after period extending 1 visit	5	192	26.04 (8.39–60.71)	6	239	25.11 (9.16–54.64)	0.96 (0.29–3.16)
Before and after period extending 2 visits	6	366	16.39 (6.00–35.68)	12	458	26.20 (13.52–45.77)	1.60 (0.60–4.25)
Before and after period extending 3 visits	9	518	17.37 (7.93–32.98)	20	683	29.28 (17.88–45.23)	1.69 (0.77–3.70)
Excludes digit and face fractures							
Before and after period extending 1 visit	5	192	26.04 (8.39–60.71)	6	239	25.11 (9.16–54.64)	0.96 (0.29–3.16)
Before and after period extending 2 visits	6	366	16.39 (6.00–35.68)	9	458	19.65 (9.00–37.30)	1.19 (0.43–3.37)
Before and after period extending 3 visits	9	518	17.37 (7.93–32.98)	15	683	21.96 (12.28–36.22)	1.26 (0.55–2.88)
Include only the wrist, arm, hip, spine, and pelvic fractures							
Before and after period extending 1 visit	3	192	15.63 (3.14–45.65)	0	239	…	…
Before and after period extending 2 visits	4	366	10.93 (2.94–27.98)	1	458	2.18 (0.29–16.10)	0.20 (0.02–1.79)
Before and after period extending 3 visits	5	518	9.65 (3.11–22.52)	3	683	4.39 (0.88–12.83)	0.5 (0.11–1.90)

*Per thousand person-years. The ellipses (…) denote incidence rates without fractures

approximately 10–30 events per 1000 person-years. Thus, the increase in fracture risk, based on the current set of analyses, is similar to the reduction in cardiovascular event risk.

Strengths and limitations of our study require consideration. The population we studied was relatively small, but we examined the question using two study designs that produced fairly similar results. These women are also at a time in their lives when blood pressure lowering becomes clinically relevant. We had a robust set of potential confounders, including many variables related to fractures that reduces the potential biases in our study. However, variables such as diabetes have a complex relationship with bone strength and fractures and could confound the relationships studied. While we used a propensity score to improve the balance across exposure groups, we could not include every variable in the propensity score. Thus, the findings of the between-group comparison are limited by any imbalance in these omitted covariates. Other strengths of this study include the representative community-based population of women. The SWAN cohort is multiethnic and from sites across the USA. Medications are collected annually, thus, there is the possibility of changes between visits. Furthermore, the SWAN cohort has rich data on potential confounders but relatively limited sample size. The number of women who started each medication of interest who fractured was small. Thus, these analyses are underpowered to detect small risks and in specific sub-groups. The small numbers of fracture events may have contributed to some inconsistency in risks across models (see Table 3). As well, there are some data that suggest that certain antidepressants, but not all, may increase the risk of fracture [13].

Many types of medications appear to affect bone metabolism and the risk of fractures. Some of the associations widely reported include corticosteroids [23], proton pump inhibitors [24], selective serotonin reuptake inhibitors [25], and opioids [26]. While many of these relationships have a strong biologic basis, some are likely not to be causal; rather, they represent associations related to confounding, i.e., patients more likely to fracture are prescribed certain medications for various indications. These relationships are even more complicated because some medications may impact fracture risk through increasing falls rather than by affecting bone metabolism, e.g., opioids. While our study has added to this literature, larger datasets with higher numbers of falls and fractures would lead to a more robust analysis.

In conclusion, we found some suggestion of an elevated risk of fracture among midlife women starting blood pressure–lowering medications. If these potential risks are real, the absolute risks may be substantial, but these risks need to be balanced with the known cardiovascular benefits of these drugs. It would be worth examining fracture risk observed in prior trials of blood pressure medications. The risk:benefit balance of medications in middle age and older adults with multiple comorbid conditions requires continued study and input from patients regarding their preferences.

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Compliance with ethical standards

Conflict of interest None.

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References

1. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH (2012) The risk of hip fracture after initiating antihypertensive drugs in the elderly. Arch Intern Med 172(22):1739–1744
2. Berry SD, Zhu Y, Choi H, Kiel DP, Zhang Y (2013) Diuretic initiation and the acute risk of hip fracture. Osteoporos Int 24(2):689–695
3. Choi HJ, Park C, Lee YK, Ha YC, Jang S, Shin CS (2015) Risk of fractures in subjects with antihypertensive medications: a nationwide claim study. Int J Cardiol 184:62–67
4. Yoshida K, Solomon DH, Kim SC (2015) Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol 11(7):437–441
5. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH (2013) The risk of falls on initiation of antihypertensive drugs in the elderly. Osteoporos Int 24(10):2649–2657
6. Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S (2011) Risk of falls associated with antihypertensive medication: self-controlled case series. Pharmacoepidemiol Drug Saf 20(8):879–884
7. Berry SD, Mittleman MA, Zhang Y, Solomon DH, Lipsitz LA, Mostofsky E, Goldense D, Kiel DP (2012) New loop diuretic prescriptions may be an acute risk factor for falls in the nursing home. Pharmacoepidemiol Drug Saf 21(5):560–563
8. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA (1999) High blood pressure and bone-mineral loss in elderly white women: a prospective study. Study of Osteoporotic Fractures Research Group. Lancet 354(9183):971–975
9. (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 265(24):3255–3264
10. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO (1991) Morbidity and mortality in the Swedish trial in old patients with hypertension (STOP-hypertension). Lancet 338(8778):1281–1285
11. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE et al (1997) Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The systolic hypertension in Europe (Syst-Eur) trial investigators. Lancet 350(9080):757–764
12. Sowers MF, Crawford S, Sternfeld B, Morganstein D, Gold EB, Greendale GA, Evans D, Neer RM, Mattews K, Sherman S et al (2000) Design, survey, sampling and recruitment methods of SWAN: a multi-center, multi-ethnic, community based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey J, Marcus M (eds) Menopause: biology and pathobiology. Academic Press, San Diego, pp 175–188
13. Gagne JJ, Patrick AR, Mogun H, Solomon DH (2011) Antidepressants and fracture risk in older adults: a comparative safety analysis. Clin Pharmacol Ther 89(6):880–887
14. Sherbourne CD, Stewart AL (1982) The MOS social support survey. Soc Sci Med 32(6):705–714
15. Baecke JA, Burema J, Frijters JE (1982) A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 36(5):936–942
16. Sternfeld B, Ainsworth BE, Quesenberry CP (1999) Physical activity patterns in a diverse population of women. Prev Med 28(3):313–323
17. Rubin DB (1997) Estimating causal effects from large data sets using propensity scores. Ann Intern Med 127(8 Pt 2):757–763
18. D'Agostino RB Jr (1998) Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 17(19):2265–2281
19. Glynn RJ, Schneeweiss S, Sturmer T (2006) Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol 98(3):253–259
20. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed 26 June 2019
21. Magaziner J, Lydick E, Hawkes W, Fox KM, Zimmerman SI, Epstein RS, Hebel JR (1997) Excess mortality attributable to hip fracture in white women aged 70 years and older. Am J Public Health 87(10):1630–1636
22. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19(4):385–397
23. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, Tenenhouse A, Reeve J, Silman AJ, Pols HA et al (2004) A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 19(6):893–899
24. Zhou B, Huang Y, Li H, Sun W, Liu J (2016) Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 27(1):339–347
25. Wu Q, Bencaz AF, Hentz JG, Crowell MD (2012) Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. Osteoporos Int 23(1):365–375
26. Miller M, Sturmer T, Azrael D, Levin R, Solomon DH (2011) Opioid analgesics and the risk of fractures in older adults with arthritis. J Am Geriatr Soc 59(3):430–438