Osteoporosis International (2018) 29:2771–2779
https://doi.org/10.1007/s00198-018-4697-0

ORIGINAL ARTICLE

Impact of prescription drugs on second fragility fractures among US Medicare patients

J. C. Munson[1,2,3] · J. P. W. Bynum[1,2,4,5] · J.-E. Bell[1,6] · C. McDonough[7] · Q. Wang[1] · T. Tosteson[1,8] · A. N. A. Tosteson[1,2]

Received: 30 March 2018 / Accepted: 3 September 2018 / Published online: 19 September 2018

Abstract

Summary Drugs that increase the risk of fracture are commonly prescribed to survivors of a fragility fracture. This study shows that starting new high-risk medications after fracture increases the risk of a second, potentially preventable fracture. For most drug classes, however, it is safe to continue medications taken before the fracture.

Introduction Most patients who survive a fragility fracture are subsequently exposed to prescription drugs that have been linked to increased fracture risk. This study was designed to quantify the extent to which current prescribing practices result in potentially preventable second fractures.

Methods We analyzed a cohort of 138,526 Medicare beneficiaries who returned to the community after a fragility fracture. Post-fracture drug use was defined using retail pharmacy fills. The risk of second fracture associated with individual drug classes was analyzed using Cox proportional hazard models. Data were further analyzed to determine whether there is a difference in risk between continuing previous therapy and initiating new therapy after fracture.

Results Many drug classes previously identified as increasing fracture risk were not associated with increased fracture risk in this cohort. Discontinuing therapy at the time of fracture was only beneficial for patients taking selective serotonin reuptake inhibitors; however, initiating therapy in previous non-users increased second fracture risk for five classes of drugs (selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, proton pump inhibitors, and non-benzodiazepine hypnotics).

Conclusion Discontinuing high-risk drugs after fracture was not generally protective against subsequent fractures. Preventing the addition of new medications may result in greater improvements in post-fracture care.

Keywords Medicare · Osteoporosis · Pharmacoepidemiology · Second fracture

Introduction

Fragility fractures among elderly Americans are common and associated with significant morbidity, mortality, and health care costs [1, 2]. Among survivors, fragility fractures are also associated with an increased risk of subsequent fractures. In one prior study, 4.3% of Medicare beneficiaries who survived a first fragility fracture went on to have a second fracture in the subsequent 12 months [3]. The burden of fragility fractures is also expected to grow with our aging population [1, 4, 5]. Effective secondary prevention of fragility fractures could therefore have important public health implications and a significant impact on health care costs.

✉ J. C. Munson
Jeffrey.C.Munson@hitchcock.org;
tamara.s.morgan@dartmouth.edu

[1] The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, USA

[2] Department of Medicine, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

[3] Department of Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Suite 5C, Lebanon, NH 03756, USA

[4] Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

[5] Institute for Health Policy and Innovation, University of Michigan, Ann Arbor, MI, USA

[6] Department of Orthopaedic Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

[7] School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, PA, USA

[8] Department of Biomedical Data Science, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Prescription drugs may represent a modifiable risk factor for effective secondary prevention of fragility fractures. Numerous studies have linked commonly prescribed drugs to an increased risk of fracture, either through increased falls or decreased bone mineral density (see Table 1 for a complete list of the drugs evaluated in this study) [6–28]. A previous report has shown that use of these medications among patients who experience a fragility fracture is common at the time of initial fracture; furthermore, use remains very common after fracture [29]. This observation raises the possibility that efforts to alter prescribing practices in the post-fracture period could positively impact the rate of second fragility fracture. Such efforts are complicated by the large number of drugs to consider and because the decision to continue or discontinue an existing therapy is clinically different than the decision to initiate new therapy in a previous non-user. Existing data are inadequate to identify which drugs are the most important to target and whether it is more important to discontinue therapy or avoid initiating a new drug.

This study was designed as a follow up to our prior work to provide practicing clinicians objective data with which to make prescribing decisions for individual drugs in patients who have experienced a fragility fracture. There were two primary objectives of this study: first, define the magnitude of second fracture risk for individual drug classes, and second, determine whether the risk associated with medication use is different among established users and new users. We hypothesized that the risk of second fragility fracture would vary among drug classes and that a small group of "highest-risk" drugs could be identified for targeted intervention. We further hypothesized that discontinuing these drugs would reduce the subsequent risk of fracture, while initiating these drugs after fracture would increase the risk of a second event.

Methods

Study cohort

The study cohort was derived from a random 40% sample of patients over age 65 enrolled in Medicare parts A (covering in-patient services) and B (covering out-patient and home health services) and eligible for part D (prescription drug benefit). From this sample, we identified US Medicare beneficiaries who sustained a fracture of the proximal femur, humerus, or distal radius between the years of 2007–2011. We excluded patients with multiple sites of fracture at initial presentation or a billing code separately indicating that the fracture was due to trauma, and patients with a diagnosis other than osteoporosis associated with excessive bone fragility (such as malignancy) that might contribute to a risk of pathological fracture.

Table 1 Frequency of high-risk[a] drug exposure 1 year post- vs. 4 months previous to fracture

Drug type	Used medications before fracture				Did not use medications before fracture			
	Continued post-fracture		Discontinued post-fracture		Initiated post-fracture		Never used	
	N	%	*N*	%	*N*	%	*N*	%
Anticonvulsants	9285	85.6	1564	14.4	6152	4.8	121,525	95.1
Antiparkinson	5715	91.4	538	8.6	2433	1.8	129,840	98.5
H2Antagonists	4651	78.5	1271	21.5	5398	4.1	127,206	95.9
Hypnotics	10,458	78.9	2800	21.1	11,964	9.6	113,304	90.5
Inhaled steroids	6588	84.0	1252	16.0	4871	3.7	125,815	96.3
Loop diuretics	24,333	89.4	2876	10.6	14,565	13.1	96,752	86.9
Nitrate antianginal agents	8634	82.1	1882	17.9	6250	4.9	121,760	95.1
Opiates	30,759	86.8	4684	13.2	62,171	60.3	40,912	39.7
Oral steroids	7308	61.3	4642	38.9	14,397	11.4	112,179	88.6
Proton pump inhibitors	30,097	90.4	3194	9.6	18,402	17.5	86,833	82.5
Second generation atypical anti-psychotics (SGAP)	4759	87.5	678	12.5	5019	3.8	128,070	96.2
Selective serotonin reuptake inhibitors (SSRI)	32,299	93.7	2219	6.4	11,247	10.8	92,761	89.2
Tricyclic antidepressants	4189	81.5	949	18.45	1984	1.5	131,404	98.5
Thiazide diuretics/thiazide-like diuretics	27,294	83.9	5241	16.1	9202	8.7	96,789	91.3
Thiazolidinedione	5484	84.8	981	15.2	1075	0.8	130,986	99.2

[a] Drugs shown in prior literature to increase the risk of incident fracture in older adults

Complete details of cohort selection and the database used for this study have been previously published [3, 29]. Fractures were identified using a combination of ICD-9 codes, codes for an appropriate radiology examination, and codes indicating treatment (surgical procedure, immobilization, or fixation.). Beneficiaries had to be enrolled in Medicare parts A and B for at least 12 months and in part D for 4 months prior to the index fracture and for the duration of follow up. In order to ensure capture of retail pharmacy claims, beneficiaries were also required to be community-dwelling at the time of fracture and for at least 30 days within the 12 months following fracture. Patients who were enrolled in hospice, who were discharged to a nursing home or rehabilitation facility without returning to the community after fracture, or who did not fill at least one prescription drug of any kind during the observation period were excluded.

Observation window for study cohort

The date a fracture was first coded in Medicare claims was used as the index date after confirming that no prior fracture at the same site had been coded in the previous 12 months. A 120-day look-back window from the index date was used to define prescription drug use prior to the fracture. Prescription drug use and subsequent fractures were recorded for 12 months following the index date. Follow-up time was censored at death.

Prescription drug use

The primary exposure in this study was use of high-risk prescription drugs in the 1 year after fracture. We used retail pharmacy fill claims from the part D prescription drug event file to define exposure to 14 drug classes that have been associated with increased fracture risk in the existing literature, listed in Table 1. We were unable to include benzodiazepines because they were not uniformly covered by part D at the time of the study. For each drug class identified, post-fracture use was treated as a time-varying variable and patients were considered exposed for the duration of a prescription as defined by the date of fill and days' supply dispensed. Pre-fracture use was defined as any prescription fill in the 120 days prior to fracture. Opiates were not included as a primary drug exposure of interest because these drugs are uniquely indicated by the fracture event; however, because of their previously documented association with fracture risk, the use of opiates was included as a confounding variable. Similarly, because of the previously documented protective effect of bisphosphonates, use of these drugs prior to fracture was included as a confounding variable.

Second fracture

The primary outcome variable was a second fragility fracture in the 12 months following the index fracture. The same definition and diagnostic criteria were used to identify both the index and subsequent fractures. We excluded second fractures associated with a diagnostic or procedure code that suggested these claims were related to a complication or revision of the initial fracture. For fractures at the same site (i.e., two claims for a humerus fracture), we required at least 90 consecutive days without a fracture claim between the two events. This requirement was implemented to avoid counting a follow-up visit for the index fracture as a second fracture. Complete details of the procedure used to identify second fractures have been published elsewhere [3].

Statistical analysis

The primary comparisons for analysis are based on the clinical options available to prescribing providers at the time of an index fracture. As outlined in Fig. 1, the relevant decisions are determined by the exposure status of the patient to a drug at the time of fracture. For patients who are not on a specific drug or drug class at the time of fracture, the only option to consider is whether or not to initiate therapy after fracture. Similarly, for patients already taking a drug at the time of fracture, the only decision is whether or not to discontinue therapy. The two clinically meaningful comparisons are therefore (1) patients who start therapy compared to those who are never users and (2) those who stop therapy after fracture compared to those who continue treatment.

To analyze the effect of post-fracture drug use on second fragility fractures, we used Cox proportional hazards models with drug exposure treated as a time-varying exposure variable. These models were adjusted for age, gender, race, bisphosphonate use prior to fracture, number of prescription drugs of any kind used at the time of fracture, and use of opiates after fracture. To control for comorbid illnesses that impact long-term survival and might affect fracture risk, we also controlled for the number of conditions included in the Charlson comorbidity index present in each individual. [30] To make the clinically relevant comparisons outlined in Fig. 1, we used an interaction term with pre-fracture drug exposure in these models to generate estimates of the effect of discontinuing (vs. continuing) therapy and of initiating (vs not initiating) therapy. After running each drug class in separate models, we identified the drugs with statistically significant effects on second fracture rates. To assess the effect of each drug class independent of other drugs that might be prescribed simultaneously, we re-ran our primary models on these drugs with the other statistically significant drugs included as potential confounders.

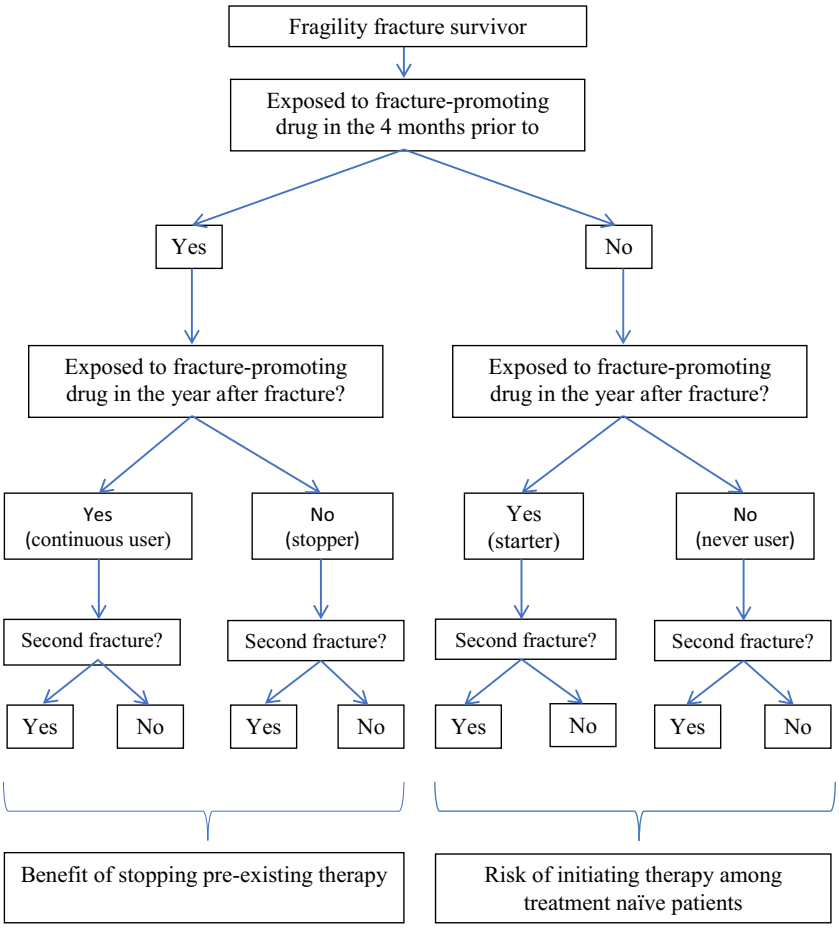

Fig. 1 Conceptual model to define the clinically relevant comparisons for post-fracture drug exposure and second fracture risk

Secondary analyses

Many of the drugs included in the list of high-risk medications may be more likely to be prescribed during a hospitalization, which in turn may reflect a greater degree of overall frailty. To assess the possibility that high-risk drugs are prescribed selectively to high-risk patients via an index hospitalization, we performed a secondary sub-analysis limited to patients who sustained a hip fracture because all of these patients were hospitalized at the time of fracture. Also, bisphosphonate use prior to fracture could modify the risk associated with high-risk medication use after fracture. To explore this possibility, we performed a second sensitivity analysis limited to patients who were non-users of bisphosphonates at the time of fracture.

Results

Demographics and post-fracture drug use

We identified 138,526 Medicare beneficiaries who experienced a fragility fracture between 2007 and 2011 and met all inclusion and exclusion criteria [3, 29]. Among this group, 7174 (5.2%) experienced a subsequent fracture in the 12 months following their index event. Table 2 shows the baseline characteristics of the total cohort. More than half of fragility fracture survivors were 80 years of age or older, and two thirds of them had at least one Charlson comorbidity. As observed in prior work [29], nearly 80% of patients were taking at least one high-risk medication at the time of their fragility fracture.

Use of prescription drugs previously associated with fracture was common in the 12 months following fracture. Examining all high-risk drugs together, 27% of users prior to fracture stopped at least one high-risk medication after the fracture event, while 16% of all fracture survivors filled at least one prescription for a new high-risk medication after fracture. Aside from opiates, the most common drugs prescribed in the post-fracture period were proton pump inhibitors, selective serotonin reuptake inhibitors, and diuretic medications, each of which was prescribed to more than 25% of the cohort.

Association of prescription drugs with second fracture

There was no consistent benefit to stopping high-risk medications among patients who were already using these medications at the time of fracture. In fact, as shown in Table 3, we observed a reduction in the risk of second fracture associated with discontinuation after fracture for only one drug class (SSRI's,

Table 2 Characteristics of fragility fracture survivors in a Medicare population (2007–2011)

	N (mean)	% (STD)
Type of fracture		
Hip (%)	66,379	47.9
Humerus (%)	21,927	15.8
Distal radius (%)	50,220	36.3
Age at time of fracture	80.07	7.6
65–69	14,414	10.4
70–74	22,744	16.4
75–79	27,207	19.6
80–84	31,951	23.1
85+	42,210	30.5
Sex female	116,923	84.4
Race		
Black	3959	2.9
Hispanic	7086	5.1
Other	127,481	92.0
Low-income subsidy	42,796	30.9
No. of comorbidities (per Charlson)		
0	46,111	33.3
1	39,556	28.6
2	25,942	18.7
3	14,524	10.5
4+	12,393	9.0
Hospitalized	73,872	53.3
Number of drugs prior to fracture*		
0–2	17,354	12.5
3–5	40,532	29.3
6–9	47,895	34.6
10–12	32,745	23.6
Discharged to rehab/SNF/SWN post-fracture	47,054	34.0
Received bisphosphonate	25,033	18.1
Received opiates within 120 days prior to fracture	35,443	25.6
Started at least one high-risk drug[a]	22,180	16.0
Used at least one high-risk drug[a] before fracture	109,345	78.9
Stopped at least one high-risk drug[a] after fracture	29,017	21.0

[a] Drugs shown in prior literature to increase the risk of incident fracture in older patients

*Number of unique prescription drugs of any kind filled in the 120 days prior to fracture

adjusted HR 0.88, 95% CI 0.81–0.96). This drug class also had the lowest rate of discontinuation (6%) among all drug classes examined (Table 3). Stopping oral corticosteroids (the drug class most likely to be discontinued) was associated with a similar reduction in risk as discontinuing SSRIs (adjusted HR 0.87) but failed to achieve statistical significance (95% CI 0.73–1.03) despite being used by nearly 9% of the population prior to fracture. At the same time, discontinuation of diuretics (loop diuretics [adjusted HR 1.19, 95% CI 1.08–1.31] and thiazide diuretics [adjusted HR 1.21, 95% CI 1.09–1.35]) was associated with an increased risk of subsequent fractures even after adjusting for other medications used and general markers of comorbidity. These results were robust in analyses limited to hip fractures and in analyses that included multiple drug categories in the same models.

Initiating high-risk medications was more consistently associated with an increased risk of second fracture. Among patients who were treatment naïve at the time of initial fracture, we found that five drug classes were associated with an increased risk of second fracture when prescribed in the 12 months after the index event (see Table 3 for complete results). These classes were sedative/hypnotic medications (HR 1.27, CI 1.08–1.48), proton pump inhibitors (HR 1.20, CI 1.08–1.33), second-generation anti-psychotics (HR 1.70, CI 1.43–2.02), selective

Table 3 Risk of second fracture related to starting, stopping, or continuing high-risk[a] prescription drugs

	Starter vs. never user		Discontinued use vs. continued use	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Anticonvulsants	1.193	0.98–1.5	1.089	0.93–1.27
Antiparkinson	1.174	0.88–1.6	0.936	0.78–1.13
H2Antagonists	1.208	0.99–1.5	1.067	0.86–1.33
Hypnotics	1.264	1.08–1.48	0.942	0.82–1.08
Inhaled steroids	0.962	0.73–1.28	1.078	0.89–1.31
Loop diuretics	1.097	0.97–1.24	1.186	1.07–1.31
Nitrate antianginal agents	0.992	0.77–1.28	0.977	0.83–1.15
Oral steroids	1.142	0.88–1.48	0.867	0.73–1.03
Proton pump inhibitors	1.192	1.07–1.33	1.001	0.91–1.10
Second generation atypical anti-psychotics (SGAP)	1.694	1.43–2.01	1.012	0.83–1.24
Selective seratonin reuptake inhibitors (SSRI)	1.834	1.64–2.05	0.878	0.81–0.96
Tricyclic antidepressants	1.628	1.19–2.22	1.167	0.93–1.46
Thiazide diuretics/thaizide-like diuretics	0.932	0.79–1.10	1.209	1.09–1.34
Thiazolidinedione	0.701	0.41–1.21	1.025	0.83–1.26

[a] Drugs shown in prior literature to increase the risk of incident fracture in older patients

serotonin reuptake inhibitors (HR 1.84, CI 1.64–2.06), and tricyclic antidepressants (HR 1.64, CI 1.20–2.23). Sedative/hypnotics, PPIs, and SSRIs were also among the most commonly initiated medications after fracture. Again, these observed associations were unchanged in analyses limited to patients with hip fracture and in analyses that controlled for all five drug classes simultaneously. Our analyses also showed reproducible effect estimates of covariates and post-fracture opiate use across all of the individual drug-class models suggesting the observed primary drug effects were not the result of differential distribution of confounders across each drug exposure populations (individual models not shown).

Results of secondary analysis among bisphosphonate non-users

When we repeated our analyses limited only to bisphosphonate non-users at the time of fracture, two new statistically significant associations were observed. In this sub-cohort, initiation of H2 antagonists was associated with an increase in fracture risk (HR 1.27, 95% CI 1.02–1.58) while discontinuation of oral corticosteroids was now associated with a reduction in subsequent fracture risk (HR 0.81, 95% CI 0.67–0.99). Additionally, the initiation of tricyclic antidepressants no longer had a significant effect on fracture risk (HR 1.29, 95% CI 0.95–2.03).

Discussion

Prevention of second fracture among those who survive an initial fragility fracture is an important goal to reduce post-fracture morbidity, mortality, and health care costs. Prescription drugs that may contribute to an increased incidence of second fracture represent an appealing target to help achieve this goal as they are commonly prescribed and commonly continued in the post-fracture setting. Our study yielded two primary findings that may be useful in secondary prevention of fracture. First, we observed that stopping high-risk medications among patients using these prior to a fragility fracture is unlikely to make a significant impact on the rate of subsequent fracture. The exception to this observation is SSRIs in which discontinuation was associated with a 12% reduction in the hazard of a subsequent fracture. Our second observation was that initiation of new high-risk medications may result in an increased risk of second fracture, but not for all drug classes previously identified as increasing the risk of incident fragility fracture.

The first observation—that stopping high-risk medications among users is generally not an effective target for intervention—was contrary to our hypothesis that careful medication reconciliation with removal of high-risk medications could significantly reduce the rate of second fractures. The reason for this observation is unclear, although there are many possible explanations. For some of these drugs, the mechanism of increased fracture risk is diminished bone mineral density. The impact of prior use on bone density is not immediately reversed by withdrawal of the causative drug, leaving the individual at continued risk long after drug cessation. It is possible the survival curves defining fracture risk would separate with longer observation for such drugs. For other drugs, the risk of fracture may be most heavily concentrated in the initial phase of use, potentially contributing to the index fracture event, but after passing through that initial period, sustained use may not be associated with

persistently elevated risk. It is also possible our study was not sufficiently powered to observe a clinically relevant change in risk, particularly for some of the less-commonly prescribed drugs and given that discontinuation of high-risk medications is relatively uncommon. However, the fact that the primary effect estimates for discontinuing therapy mostly center closely around an HR of 1.0 argues against this possible explanation.

Our second finding suggests there is a small group of medications that should not be initiated in the post-fracture period. Three of these classes (proton pump inhibitors, selective serotonin reuptake inhibitors, and hypnotics) were prescribed to more than 15% of all fracture survivors and to at least 10% of prior non-users in the year following fracture, suggesting there is an opportunity to impact a large number of patients by targeting a relatively small number of high-risk drugs. Our results further suggest that avoiding drug exposure rather than substituting a different agent may be the preferred course when feasible. For instance, histamine receptor antagonists (H2RA), generally considered a safer substitute for PPI therapy, had an HR for second fracture (HR = 1.21) that was nearly identical to that of PPIs, with a confidence interval that nearly achieved conventional cutoffs for statistical significance (95% CI 0.99–1.48). This wider confidence interval at least in part reflects the fact that these drugs are less commonly prescribed than PPIs. Although firm conclusions cannot be drawn from this finding, the data suggest it is at least possible that a large-scale transition to H2RA use from PPI use may not have the desired effect of significantly reducing the incidence of second fracture. Similarly for SSRIs, tricyclic antidepressant therapy is also associated with an increase in the risk of subsequent fracture and would not be an appropriate substitute.

Our results in new users are consistent with the literature that has previously identified these drug classes as high-risk; however, for several other drug classes (thiazide diuretics, inhaled corticosteroids, nitrate-based anti-anginal drugs, and thiazolidinediones), we did not observe even a trend towards increased risk when focused on second fracture. The lack of association may be due to differences in risk in a population of patients who already experienced a fracture and as a result have a different underlying risk factor and illness profile from the general population more typically studied. For the remaining classes, we observed HR estimates between 1.10 and 1.21, suggesting a possible increased risk of fracture, but with confidence intervals that crossed 1. Given our very large sample size, these findings suggest that these drugs are uncommonly prescribed and that even if an effect exists for these drugs, focusing efforts on improved prescribing behavior may be better directed at other target drugs.

Our finding that initiation of high-risk medications is associated with higher second fracture risk than continued use is also consistent with literature that suggests fracture risk may not be linear over time. This has been observed most commonly in anti-hypertensive therapy, with data demonstrating the fracture risk is highest shortly after treatment initiation or titration [25, 27, 31]. Our study extends this observation to other drug classes and suggests that an attenuation of long-term risk may explain why continuation of pre-existing therapy is not associated with high rates of second fracture. Our study is also consistent with a prior study by Harstedt and colleagues which demonstrated that prescription drug exposure may be an important risk factor for hospital re-admission among hip fracture survivors [32]; however, to our knowledge, our study is the first to differentiate continuation from initiation of medications following a fracture event.

The results of our secondary analysis limited to bisphosphonate non-users should prompt continued research. These results suggest bisphosphonate non-users may be at higher risk from fracture when starting H2 receptor antagonists or when continuing to take oral corticosteroids. Although the change in effect from our primary analysis was not large, these results support continued investigation into the potential role of bisphosphonates and other fracture prevention strategies in attenuating the risk associated with post-fracture prescribing decisions.

Our study has several potential limitations. We used data from 2007 to 2011, which would impact our ability to observe trends in either prescribing or fracture risk that have evolved in the past 6 years. Having said that, improvement campaigns in the intervening years have focused on osteoporosis treatment rather than changing exposure to medications that may increase fracture risk [33, 34]. The age of our data also precludes examination of benzodiazepines which were excluded from part D coverage until after the last year of the study cohort. Nevertheless, it is unlikely that this omission would alter our principal finding that initiation of new drugs is a more important target for secondary prevention than focusing on discontinuation of drugs previously prescribed. Our analyses also focused on single drug exposure-outcome relationships. This approach may mask important synergistic effects of drug combinations. Evaluating these drug combinations was beyond the scope of this initial work but would be a fruitful area for further investigation. Our data are also limited to patients enrolled in Medicare part D. These patients have a higher rate of comorbidity compared to the general Medicare population which may limit the generalizability of our findings [35]. Our study included patients discharged to skilled nursing facilities for rehabilitation prior to returning to the community; however, we excluded patients who are or become permanent residents of nursing homes after fracture. This population is likely to have a different level of comorbid illness, different levels of social support and medical supervision, and are often treated by a different population of prescribing physicians. Additionally, because nursing home patients generally have a poorer prognosis and more significant comorbidities, prescribing decisions may appropriately be less influenced by measures of long-term fracture risk, the subject of this study. For these reasons, our results may not be applicable to this

population. Lastly, we can only evaluate potential confounding variables that are observable in claims; other unobservable variables, such as the severity of comorbid diseases, might cause a spurious association between the drugs selected and second fracture. Our decision to use a cohort of patients with prior fracture mitigates this limitation to a certain degree, because each individual in our study has demonstrated that they are at high risk for fracture relative to a cohort of patients without fracture. In this way, the fact that they have previously suffered a fragility fracture is an effective marker for all of their measured and unmeasured risk factors for the outcome of interest. Additionally, our subgroup analyses limited to patients with hip fracture suggested that our observed associations were not being mediated by the event of hospitalization and associated prescribing behaviors.

Conclusion

Our study demonstrates that attention to the use of high-risk medications may reduce the incidence of second fracture. Counter to our initial hypothesis, however, our data suggest interventions should focus on preventing initiation of high-risk medications rather than on discontinuing ongoing therapy.

Funding information The Multidisciplinary Center for Musculoskeletal Diseases at Dartmouth is funded by the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS P60 AR062799; Anna N.A. Tosteson, PI).

Compliance with ethical standards

Conflicts of interest None.

References

1. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A (2007) Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 22(3):465–475
2. Ray NF, Chan JK, Thamer M, Melton LJ 3rd (1997) Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res 12(1):24–35
3. Bynum JP, Bell JE, Cantu RV et al (2016) Second fractures among older adults in the year following hip, shoulder, or wrist fracture. Osteoporos Int 27:2207–2215
4. (2004) Bone health and osteoporosis: a report of the surgeon general. US Department of Health and Human Services, Rockville
5. Omsland TK, Magnus JH (2014) Forecasting the burden of future postmenopausal hip fractures. Osteoporos Int 25(10):2493–2496
6. De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, Van Staa TP (2007) Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis Rheum 56(1):208–214
7. Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM (2009) Thiazolidinediones and fractures in men and women. Arch Intern Med 169(15):1395–1402
8. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, Schwartz AV, Hanlon JT, Nevitt MC, Study of Osteoporotic Fract (2002) Central nervous system-active medications and risk for falls in older women. J Am Geriatr Soc 50(10):1629–1637
9. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B (1998) Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. Am J Epidemiol 148(9):887–892
10. Hubbard R, Tattersfield A, Smith C, West J, Smeeth L, Fletcher A (2006) Use of inhaled corticosteroids and the risk of fracture. Chest 130(4):1082–1088
11. Hugenholtz GW, Heerdink ER, van Staa TP, Nolen WA, Egberts AC (2005) Risk of hip/femur fractures in patients using antipsychotics. Bone 37(6):864–870
12. Johannes CB, Schneider GA, Dube TJ, Alfredson TD, Davis KJ, Walker AM (2005) The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. Chest 127(1):89–97
13. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, Kravitz BG, Yu D, Heise MA, Aftring RP, Viberti G, for the A Diabetes Outcome Progression Trial (ADOPT) Study Group (2008) Rosiglitazone-associated fractures in type 2 diabetes: an analysis from a diabetes outcome progression trial (ADOPT). Diabetes Care 31(5):845–851
14. Lee TA, Weiss KB (2004) Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 169(7):855–859
15. Leipzig RM, Cumming RG, Tinetti ME (1999) Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 47(1):30–39
16. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ 3rd (1987) Psychotropic drug use and the risk of hip fracture. N Engl J Med 316(7):363–369
17. Ray WA, Thapa PB, Gideon P (2000) Benzodiazepines and the risk of falls in nursing home residents. J Am Geriatr Soc 48(6):682–685
18. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, Goltzman D, Canadian Multicentre Osteoporosis Study Research Group (2007) Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med 167(2):188–194
19. Schneeweiss S, Wang PS (2004) Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. J Clin Psychopharmacol 24(6):632–638
20. Shorr RI, Griffin MR, Daugherty JR, Ray WA (1992) Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. J Gerontol 47(4):M111–M115
21. Takkouche B, Montes-Martinez A, Gill SS, Etminan M (2007) Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf 30(2):171–184
22. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C (2000) Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford) 39(12):1383–1389
23. Vestergaard P, Rejnmark L, Mosekilde L (2006) Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. Osteoporos Int 17(6):807–816
24. Yang YX, Lewis JD, Epstein S, Metz DC (2006) Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 296(24):2947–2953
25. 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
26. Ruths S, Bakken MS, Ranhoff AH, Hunskaar S, Engesaeter LB, Engeland A (2015) Risk of hip fracture among older people using antihypertensive drugs: a nationwide cohort study. BMC Geriatr 15:153

27. Shimbo D, Barrett Bowling C, Levitan EB, Deng L, Sim JJ, Huang L, Reynolds K, Muntner P (2016) Short-term risk of serious fall injuries in older adults initiating and intensifying treatment with antihypertensive medication. Circ Cardiovasc Qual Outcomes 9(3):222–229
28. Tolppanen AM, Taipale H, Tanskanen A, Tiihonen J, Hartikainen S (2016) Comparison of predictors of hip fracture and mortality after hip fracture in community-dwellers with and without Alzheimer's disease—exposure-matched cohort study. BMC Geriatr 16(1):204
29. Munson JC, Bynum JP, Bell JE et al (2016) Patterns of prescription drug use before and after fragility fracture. JAMA Intern Med 176(10):1531–1538
30. Radley DC, Gottlieb DJ, Fisher ES, Tosteson AN (2008) Comorbidity risk-adjustment strategies are comparable among persons with hip fracture. J Clin Epidemiol 61(6):580–587
31. Torstensson M, Hansen AH, Leth-Moller K et al (2015) Danish register-based study on the association between specific cardiovascular drugs and fragility fractures. BMJ Open 5(12): e009522
32. Harstedt M, Rogmark C, Sutton R, Melander O, Fedorowski A (2016) Polypharmacy and adverse outcomes after hip fracture surgery. J Orthop Surg Res 11(1):151
33. Association AO (2018) Own the bone. http://www.ownthebone.org/. Accessed Feb 9, 2018
34. Assurance NCfQ (2017) Osteoporosis testing and management in older women. Washington, DC
35. Munson JC, Morden NE, Goodman DC, Valle LF, Wennberg JE (2013) The Dartmouth Atlas of medicare prescription drug use. The Dartmouth Institute for Health Policy and Clinical Practice