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Impact of the US Food and Drug Administration's safety-related announcements on the use of bisphosphonates after hip fracture

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- Data collection: SCK, HM, WE
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SCK receives research grants to the Brigham and Women's Hospital from Pfizer, AstraZeneca, Genentech, and Lilly.

DHK provides paid consultative services on geriatrics care to the Alosa Foundation, a non-profit educational organization with no relationship to any drug or device manufacturers.

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Authors' Contributions: SCK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SCK is the guarantor of this work. SCK is responsible for the concept and design of the study, the acquisition of data and the analysis and interpretation of data. SCK drafted and finalized the manuscript. DHK, JMP and DHS are responsible for the concept and design of the study, the interpretation of data and critical revision of the manuscript. HM is responsible for the design of the study, the analysis of data and critical revision of the manuscript. WE and JMF are responsible for the design of the study, the analysis and interpretation of data, and critical revision of the manuscript. All authors approved the final version of the manuscript.

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Abstract

The U.S. FDA issued several announcements related to potential risk of bisphosphonates including osteonecrosis of the jaw (2005), atrial fibrillation (2007) and atypical femur fracture (2010). We aimed to evaluate the impact of three FDA drug safety announcements on the use of bisphosphonates in patients with hip fracture using claims data from a U.S. commercial health plan (2004–13). We calculated the proportion of patients in each quarter who received a bisphosphonate or other osteoporosis medication in the 6 months following hospitalization for hip fracture. Segmented logistic regression models examined the time trends. Among 22,598 patients with hip fracture, use of bisphosphonate decreased from 15% in 2004 to 3% in the last quarter of 2013. Prior to the 2007 announcement, there was a 4% increase in the odds of bisphosphonate use every quarter (OR 1.04, 95%CI 1.02–1.07). After the 2007 announcement, there was a 4% decrease in the odds of bisphosphonate use (OR 0.96, 95%CI 0.93–0.99) every quarter. The announcement in 2007 was associated with a significant decline in the rate of change of bisphosphonate uses over time ($p < 0.001$), but no impact on other osteoporosis medication use ($p = 0.2$). After the 2010 announcement, the odds of bisphosphonate use continued to decrease by 4% (OR 0.96, 95%CI, 0.94–0.98) each quarter and the odds of other osteoporosis medication use remained stable over time (OR 0.99, 95%CI 0.96–1.02). The FDA safety announcement related to atrial fibrillation in 2007 was significantly associated with a decrease in bisphosphonate use among patients with hip fracture.

INTRODUCTION

Bisphosphonates are the first-line therapy for treatment of osteoporosis. While current guidelines recommend use of pharmacologic treatment including bisphosphonates for the secondary prevention of hip fracture,[1] the rate of post-fracture osteoporotic treatment has been suboptimal and decreasing.[2 3] Patients' and clinicians' concerns over potential side effects of bisphosphonates may explain this decline, at least in part. Over the past decade, the U.S. Food and Drug Administration (FDA) has issued several safety alerts or announcements related to potential risk of bisphosphonates including osteonecrosis of the jaw (ONJ) in May 2005, atrial fibrillation in October 2007, and atypical femur fracture in March 2010.[4 5]

While it is important to recognize potential side effects of bisphosphonates, the benefits of bisphosphonates outweigh harms in post-osteoporotic fracture patients. The occurrence of ONJ was rare and mostly noted in patients using high dosages of bisphosphonates for cancer, rather than osteoporosis.[6 7] The risk of atrial fibrillation was initially reported to be greater in the zoledronic acid group versus placebo (1.3% vs.0.5%, $p < 0.001$) in the HORIZON-PFT trial,[8] but the risk does not appear to be increased in oral bisphosphonate users based on a recent meta-analysis of 26 randomized controlled trials.[9] The risk of

atypical femur fracture is increased with use of bisphosphonates, particularly the long-term use, but it is also rare; current estimates suggest that it occurs in 3 to 50 cases per 100,000 person-years of bisphosphonate users.[10 11] Since it is likely that these side effects of bisphosphonates received more media attention after the FDA safety announcements compared with the known benefits of these drugs in patients who sustained osteoporotic fracture, we hypothesized that the FDA safety announcements would have a negative impact on the use of bisphosphonates among patients with hip fracture in the U.S.

The objectives of this study were 1) to evaluate the trend in the use of bisphosphonates and other osteoporosis medications in patients following hospitalization for hip fracture over the past decade and 2) to examine whether the three aforementioned FDA drug safety announcements had an impact on the trend in use of bisphosphonates and other osteoporosis medications in the post-hip fracture patient population.

MATERIALS AND METHODS

Data Source

Data were collected from a large U.S. commercial health plan, United HealthCare, between 2004 and 2013. This plan insures primarily working adults and their family members. The database contains demographic information, health plan enrollment status and longitudinal claims information including medical diagnoses and procedures from inpatient and outpatient medical encounters -- coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM), and Current Procedural Terminology, Fourth Edition - and pharmacy dispensing on its approximately 14 million subscribers across the U.S. on a yearly basis. The quality of these data on inpatient diagnoses, procedures, health care utilization and drug dispensing as well as some outpatient diagnoses is known to be high.[12]

Study Cohort

We identified all adults aged 50 years who had a hospitalization for hip fracture based on a combination of ICD-9 and procedure codes.[3] This claims-based algorithm was shown to have a positive predictive value over 95% for hip fracture. [13] The date of hospitalization for hip fracture was defined as the index date. The primary outcome of interest was the proportion of patients in each quarter who received an oral or intravenous bisphosphonate (i.e., alendronate, risedronate, ibandronate, or zoledronic acid) in the 6 months after the index date. The secondary outcome of interest was the proportion of patients in each quarter who received any non-bisphosphonate osteoporosis medication (i.e., calcitonin, hormone replacement therapy, raloxifen, teriparatide, or denosumab) in the 6 months after the index date. Because of the long duration of treatment effect, we excluded patients who received zoledronic acid prior to the index date.

Data Analysis

We assessed a number of variables related to the risk of hip fracture and use of osteoporosis medication data from the 180-day baseline period before the index date. These variables included demographic characteristics, presence of comorbidities, comorbidity index, [14]

use of bisphosphonate or other osteoporosis medication at baseline, and health care utilization factors (Table 1 for details). We compared these variables between patients who received a bisphosphonate and those who did not in the 6 months following hospitalization for hip fracture. We calculated the proportion of patients who died within a year following hospitalization for hip fracture. During the 10-year study period, we calculated the proportion of patients who received a bisphosphonate or other osteoporosis medications in the 6 months following hospitalization for hip fracture over time. We used segmented logistic regression to examine the impact of three FDA announcements on use of bisphosphonates over calendar time. The model included an initial intercept, four slope terms that described the trend in use of bisphosphonates before and after each FDA announcement, and 3 terms for step changes at the time of the announcements. As a negative control, these steps were repeated for the secondary outcome of interest defined as the proportion of patients who received other osteoporosis medications in the 6 months following hospitalization for hip fracture each quarter. All analyses were performed using SAS 9.3 and Stata 13. The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital. Patient informed consent was not required, as the dataset was de-identified.

RESULTS

There were a total of 22,598 patients who were hospitalized with hip fracture. The mean (SD) age was 72.4 (10.8) years and 68% were female. Of these, 3,273 (14.5%) received a bisphosphonate in the 6 months after the index date. Patients who received a bisphosphonate after the index date were more likely to be older and female and have a diagnosis of osteoporosis and a greater number of comorbidities at baseline compared with those who did not receive a bisphosphonate. Prior to the index date, 26% had at least one fracture at any location and 11% received at least 1 dispensing for bisphosphonates. Table 1 describes patient characteristics at baseline. During the year following hospitalization for hip fracture, a total of 3,930 (17%) patients, 10% of those who received a bisphosphonate after hip fracture and 19% of those who did not, died.

Over the study time period, the proportion of patients who filled at least one prescription for a bisphosphonate or received at least one intravenous administration following hip fracture decreased from 15% in 2004 to 3% in the last quarter of 2013, while the proportion of other osteoporosis medication use was stable around 5% over time (Figure 1). Until the last quarter of 2007 when the FDA issued the 2nd announcement related to the risk of atrial fibrillation, there was a 4% increase in the odds of bisphosphonate use after hip fracture every quarter [odds ratio (OR) 1.04, 95% CI 1.02–1.07]. Between 2008 and 2010, there was a 4% decrease in the odds of bisphosphonate use (OR 0.96, 95% CI 0.93–0.99) every quarter. The 2nd announcement in 2007 was associated with a significant change in the trend of bisphosphonate uses over time ($p < 0.001$), but it had no impact on the trend of other osteoporosis medication use over time ($p = 0.2$). After the 1st quarter of 2010 following the 3rd FDA announcement related to risk of atypical femur fracture, the odds of bisphosphonate use following hip fracture continued to decrease by 4% (OR 0.96, 95% CI, 0.94–0.98) each quarter but the odds of other osteoporosis medication use continued to have a non-significant trend over time (OR 0.99, 95% CI 0.96–1.02).

DISCUSSION

This population-based longitudinal study showed that use of bisphosphonate decreased from 15% in 2004 to 6% in 2013 in patients following hospitalization for hip fracture. We also found that the FDA safety announcement related to the risk of atrial fibrillation in 2007 was associated with a significant decline in the use of bisphosphonates over the study period.

The results of this study call attention to several issues related to management of osteoporosis in general as well as secondary prevention of osteoporotic fracture. First, it is concerning that not even 10% of patients receive a bisphosphonate for the secondary prevention of osteoporotic fracture in more recent years. It is well-known that patients who sustain a hip fracture are at an increased risk for recurrent hip or other osteoporotic fractures. [15] An Italian study showed that over 4% of patients with a hip fracture develop a fracture in the contralateral femur with a 1-year refracturing rate of 2.4%. [16] In another study of 549 elderly patients with hip fracture, the rate of any subsequent self-reported fracture after the initial hip fracture was 10.4 per 100 person-years. [17] Starting from such a low level of post-fracture treatment, any reduction in osteoporosis treatment rates exacerbates an existing public health concern.

Second, despite well-established evidence on the effectiveness of these agents, the FDA safety announcements appear to have a negative impact on the use of oral or intravenous bisphosphonates in clinical scenarios with very strong indication for treatment. [18 19] While the FDA is responsible for timely updates of the public with potential safety issues related to previously approved drugs, their safety communications must be considered in the appropriate public health context. The FDA's mandate is for assuring the safe use of drugs, but a more balanced approach may have recognized that osteoporosis treatments post-fracture are under-utilized despite strong recommendations. One hopes that this consideration might have led to a more balanced approach to discussing large benefits versus rare risks of these agents.

Furthermore, when the FDA or others describe potential side effects of a drug, it is critical to report an absolute risk as well as a relative risk. For example, a study that analyzed three randomized controlled trials of bisphosphonates nicely summarized their findings that treating 1,000 women with osteoporosis for 3 years with a bisphosphonate will prevent approximately 100 vertebral or non-vertebral fractures (number needed to treat: 10) while it will cause 0.3 to 1.4 atypical femur fractures assuming the relative risk ranges from 1.5 to 3.0 (number needed to harm: 714–3333). [20] This type of information allows for making a well-informed and balanced treatment decision.

The current study has limitations. First, we were unable to study reasons why patients did not receive a bisphosphonate following hospitalization for hip fracture. Several factors such as patient or physician preference, contraindications to bisphosphonates or frailty may have affected the treatment decision not to start a bisphosphonate. Second, there is a potential for misclassification of hip fracture. While we use a previously validated algorithm to identify patients with hip fracture, the algorithm was not validated in this study database. Third, because this study is based on a commercially insured patient cohort, our results may not be

generalizable to uninsured or underinsured patients. The underuse of bisphosphonates for the secondary prevention of osteoporosis fracture may be worse in other populations. Fourth, our study cannot imply causal association between the FDA safety announcements and a decrease in the use of bisphosphonates.

In conclusion, over the past decade, use of bisphosphonates following hospitalization for hip fracture has substantially decreased. Our study found that the FDA safety announcement related to atrial fibrillation in 2007 was significantly associated with a decrease in trend of bisphosphonate use in patients with hip fracture. Given the clinical importance of the secondary prevention of hip fracture, these results highlight the need to weigh benefits versus harms of bisphosphonates and to improve the communication of drug safety information with both clinicians and patients.

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- Mogun, Eddings, Polinski, and Franklin have nothing to disclose.
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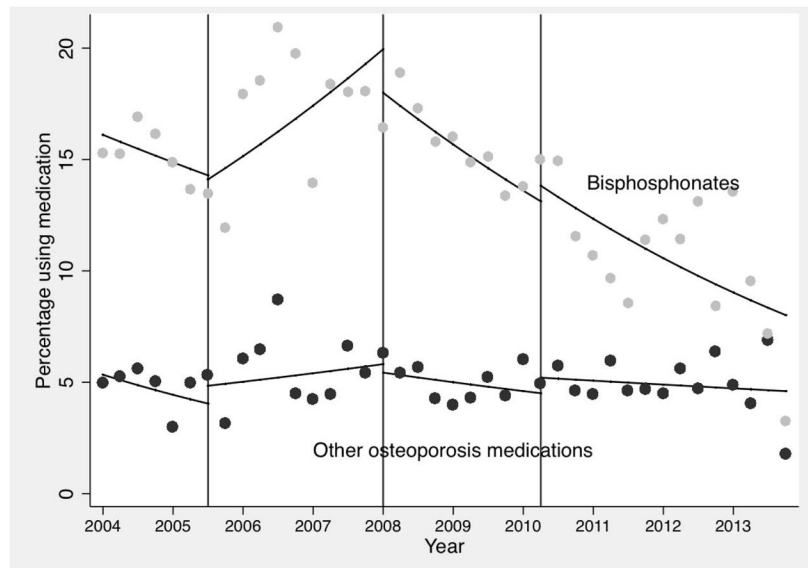


Figure 1. Impact of FDA safety announcements on the use of osteoporosis medications following hip fracture

Dots represent the observed values. The solid lines are the predicted values from the regression models fit to the person-level data. Three vertical lines indicate the quarters immediately after the three FDA announcements (far left for osteonecrosis of the jaw, middle for atrial fibrillation and far right for atypical femur fracture) were released.

Table 1

Patient characteristics in 180 days prior to hospitalization for hip fracture

	Total	Received a bisphosphonate following hip fracture		P-value
		Yes	No	
N	22,598	3,273	19,325	
<i>Demographics</i>				
Age (mean \pm SD), yr	72.4 \pm 10.8	70.9 \pm 10.6	72.6 \pm 10.8	<0.0001
Female	67.9%	86.2%	64.8%	<0.0001
<i>Comorbidities</i>				
Prior fall	6.2%	6.2%	6.2%	1.00
Prior fracture	25.9%	30.1%	25.2%	<0.0001
Osteoporosis diagnosis	10.8%	22.4%	8.8%	<0.0001
Comorbidity index ^a (mean \pm SD)	5.4 \pm 20.3	7.3 \pm 24.6	5.0 \pm 19.5	<0.0001
<i>Medications</i>				
Any bisphosphonates	10.7%	48.1%	4.4%	<0.0001
Alendronate	6.6%	29.7%	2.7%	<0.0001
Other osteoporosis drugs	16.9%	55.2%	10.4%	<0.0001
<i>Health care utilization</i>				
Acute hospitalization	17.6%	16.6%	17.7%	0.12
No. of outpatient visits	4.5 \pm 4.8	5.3 \pm 5.5	4.3 \pm 4.6	<0.0001

^aThe range of combined comorbidity score is -2 to 26.

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