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Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: a population-based cohort study

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Abstract

Summary To better understand the risk of secondary vertebral compression fracture (VCF) following a vertebroplasty or kyphoplasty, we compared patients treated with those procedures to patients with a previous VCF. The risk of subsequent fracture was significantly greater among treatment patients, especially within 90 days of the procedure.

Introduction Predominantly uncontrolled studies suggest a greater risk of subsequent vertebral compression fractures (VCFs) associated with vertebroplasty/kyphoplasty. To further understand this risk, we conducted a population-based retrospective cohort study using data from a large regional health insurer.

Methods Administrative claims procedure codes were used to identify patients receiving either a vertebroplasty or kyphoplasty (treatment group) and a comparison group of patients with a primary diagnosis of VCF who did not receive treatment during the same time period. The main outcomes of interest, validated by two independent medical record reviewers, were any new VCFs within (1) 90 days, (2) 360 days, and (3) at adjacent vertebral levels. Multi-variable logistic regression examined the association of vertebroplasty/kyphoplasty with new VCFs.

Results Among 48 treatment (51% vertebroplasty, 49% kyphoplasty) and 164 comparison patients, treated patients had a significantly greater risk of secondary VCFs than comparison patients for fractures within 90 days of the procedure or comparison group time point [adjusted odds ratio (OR)=6.8; 95% confidence interval (CI) 1.7–26.9] and within 360 days (adjusted OR=2.9; 95% CI 1.1–7.9).

Conclusions Patients who had undergone vertebroplasty/kyphoplasty had a greater risk of new VCFs compared to patients with prior VCFs who did not undergo either procedure.

Keywords Bone cement · Kyphoplasty · Osteoporosis · Population-based · Vertebral compression fractures · Vertebroplasty

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Introduction

Vertebroplasty and kyphoplasty are minimally invasive procedures for treatment of vertebral compression fractures (VCF) that involve the percutaneous instillation of bone cement (most commonly polymethylmethacrylate) into a fractured vertebra [1]. Although these procedures have been used since the 1980s primarily for pain relief and

restoration of vertebral body height, there is little evidence of their longer-term safety from either randomized controlled trials or controlled observational studies [2–4]. Limited biomechanical testing data and several small uncontrolled studies suggest that fractured vertebrae treated with bone cements are stiffer than untreated vertebrae and thus may transfer greater load to adjacent vertebral levels [5, 6]. Thus, there is concern that these procedures could lead to a heightened rate of subsequent VCFs.

Using a retrospective cohort study design of persons who received either vertebroplasty or kyphoplasty compared to persons with confirmed VCFs who were not treated with either procedure, we examined whether vertebroplasty and kyphoplasty were associated with a higher risk of secondary VCFs both at any site and at adjacent vertebrae.

Materials and methods

Treatment group

A group of treated patients, having at least one vertebroplasty or kyphoplasty procedure from January 1, 2003 to June 30, 2004, were identified based on Current Procedural Terminology (CPT)-4 codes or Healthcare Common Procedure Coding System (HCPCS) codes (Appendix) from the administrative claims data of a large regional not-for-profit health care insurer, Blue Cross and Blue Shield of Alabama, with over 3 million enrollees. Administrative data included information on inpatient, outpatient, and physician claims as well as patient demographics. Based on review of the longitudinal profiles, we defined an *index event* for a treated patient (18 years or older at the time) as their incident procedure during the study period.

To create a cohort with an incident procedure, patients with confirmed vertebroplasty or kyphoplasty from January 2001 through December 31, 2002 (run-in period) were excluded. Exclusions for cancer also were applied using administrative data (see Appendix).

In order to be as representative as possible, we included procedure claims that were both paid and rejected by the insurer. Patients were excluded if medical record reviews could not confirm the procedure or the baseline VCF or if the VCFs were a consequence of high trauma fractures (i.e., motor vehicle accidents), primary bone tumors, or metastatic cancer.

Comparison group

We also constructed a comparison group of patients with at least one VCF within the same 18-month study period, but without evidence of a vertebroplasty or kyphoplasty procedure. The comparison group, identified from claims data, included all patients 18 years of age or older at the time of the index date, with primary diagnoses of VCF based on International Classification of Disease (ICD-9) codes (Appendix) during the study period used for the treatment patients. Neither potential treatment nor comparison patients were excluded for VCF diagnoses during the run-in period. Due to the large number of treatment patients with a diagnostic code for pathologic fracture (ICD-9 code 733.13) but no evidence of cancer in the claims data, we included this diagnosis for comparison patients as well. Patients with the same contraindications as the treatment patients were excluded using both the claims data (see Appendix) and the medical record review. To enhance the comparability of the comparison and treatment groups and to control for the relevant confounding factor of age, we initially matched each treatment patient with eight comparison patients by age (±5 years). Similar to the treatment group, we defined an index event for a comparison patient as their incident VCF diagnosis during the study period.

Medical record reviews

To confirm the vertebroplasty/kyphoplasty procedures for the treatment patients, after identifying patients using administrative data, the health care insurer requested medical records documenting patient histories, physical exams, and procedure notes from the appropriate hospital, outpatient facility, or physician's office. For both the treatment and comparison cohorts, all radiological reports (spinal radiology, magnetic resonance imagery, computerized tomography, and/or bone scans) following the index event were requested to determine the diagnosis/sites of possible subsequent VCFs during the study time period. Three follow-up phone requests, approximately 3 to 4 weeks apart, were made to non-responsive facilities in an effort to collect all appropriate records. Medical records were independently reviewed by two investigators (AM, RN) for details on the vertebroplasty/kyphoplasty procedure, diagnosis and location of treatment fracture, history of other fractures, comorbidities, and other osteoporosis treatment. Based on the radiology report, fractures occurring at the index event (index fractures) were classified as either incident or prevalent fractures. A subsequent VCF was only validated in the comparison group if the location of the index fracture was available in medical records. Any discordance in record reviewers was adjudicated by consensus of a physician panel of co-authors. The review protocol was established prior to review of records, and the medical record data was abstracted into a customized version of a MedQuest database (developed by Fu and associates under contract from the Health Care Financing Administration).

Outcomes of interest, explanatory variables, and key co-variates

The main outcome of interest was a subsequent VCF following the index event. Since the vertebra receiving vertebroplasty/kyphoplasty is unlikely to be diagnosed as having a progression of an existing fracture, our primary analysis was restricted to new VCFs occurring at a different level than the baseline fracture. Because we wished to allow for the possibility that the treatment mitigates same-level fractures, a secondary analysis included the progression (worsening) of VCFs at the same vertebral level (progressive fracture) among the comparator patients. Separate analyses also examined adjacent-level fractures. The date of the subsequent VCF was defined as the first time the fracture was described in the available radiology reports following the index event. Because of concern about censoring due to patient death and other losses to follow-up that are not captured by administrative data, we evaluated this outcome at two separate time periods, 90 and 360 days after the index event. The key explanatory variable was whether patients received vertebroplasty/kyphoplasty or not.

Other variables examined included patient demographics (i.e., age and sex), frequency of administrative claims for outpatient and physician visits, and comorbidities. Using ICD-9 primary and secondary diagnosis codes available in claims data during the period from 180 days prior to and 90 days post the index date, we created a count for each patient of 30 comorbid indicators based on the work by Elixhauser et al. [7] (see Table 1) and a separate indicator of an osteoporosis diagnosis (ICD-9 code: 733.0X) prior to their index date. In addition, we looked at the site, age, and number of baseline fractures based on the radiology reports.

Statistical analysis

Univariate descriptive statistics first examined the association of vertebroplasty and kyphoplasty (considered together) with outcomes of interest. We then used multivariable logistic regression to adjust for potential confounding factors. Final models included adjustment for number of comorbidities, indicator of osteoporosis diagnosis prior to index date, sex, and age. To assess a potentially greater rate of subsequent VCFs among persons hospitalized with this condition or among VCFs characterized as new by a radiologist, we performed sensitivity analyses on these subsets. SAS software (version 9.1) was used for all statistical analyses (SAS Institute, Cary, NC, USA).

Results

Using administrative claims data, we identified 132 patients who had a CPT-4 or HCPCS code for a vertebroplasty or

Table 1 Baseline characteristics of patients in vertebroplasty/kyphoplasty treatment and comparison groups

	Treatment (*n*=48)	Comparison (*n*=164)	*p* value
Sex, % men	16 (33%)	71 (43%)	0.2
Age, years	62.1±12.2	63.7±12.0	0.4
Osteoporosis diagnosis in the 180 days prior to index[a]	13 (27%)	32 (20%)	0.2
Number of physician visits in the 180 days prior to index	5.19±5.92	5.28±5.88	0.9
Number of comorbidities[b]	3.8±2.9	3.6±3.2	0.7
Baseline/treatment fracture sites			
Thoracic spine	25 (52%)	73 (45%)	0.1
Lumbar spine	22 (46%)	69 (43%)	
Both	1 (2%)	20 (12%)	
Number of vertebral fractures at Baseline			
1	30 (63%)	111 (68%)	0.7
2–3	15 (31%)	42 (26%)	
>3	3 (6%)	10 (6%)	
Age of vertebral fractures at baseline			
New	26 (54%)	63 (39%)	<0.05
Old	3 (6%)	39 (24%)	
Unable to determine	19 (40%)	60 (37%)	

n, (percent) or mean±SD. [a] Index = incident vertebroplasty/kyphoplasty procedure for a treatment patient; incident VCF diagnosis for a comparison patient

[b] Disease count using administrative claims for the following 30 comorbidities: congestive heart failure, arrhythmias, valvular disease, pulmonary disease, peripheral vascular disease, hypertension, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, diabetes with chronic complications, hypothyroidism, renal failure, liver disease, peptic ulcer disease, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, chronic blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression.

kyphoplasty procedure during the study time period (Fig. 1). Of these 132 patients, we retrieved medical records for 95 (72%) of the patients. After medical record review, a total of 48 (51% of those with available medical records) patients met the criteria for inclusion in treatment group. Using administrative claims data from the same time period, a total of 380 patients with a primary ICD-9 code for a VCF were identified for the comparison group. Of these 380 patients, we obtained radiology records for 316 (83%) of them, and we confirmed an eligible VCF by medical record review for 164 (52%) patients that met the other criteria for the comparison group. Concordance of medical record findings among reviewers was 85.7%.

Characteristics of treatment and comparison groups are shown in Table 1. The comparison group non-significantly trended toward being slightly older and was more likely to be men. Treatment patients trended toward being more likely to have an osteoporosis diagnosis prior to the index date. Patients in each group had similar comorbidity profiles, with a mean comorbidity count of just less than four. Just over half of the fractures treated with vertebroplasty/kyphoplasty were in the thoracic spine, and one patient in the treatment group had treatment in both the thoracic and lumber spine (T12 and L1). The number of prevalent VCFs was similar in both groups (mean number of baseline fractures=1.71±0.99 in treatment group vs. 1.61±1.17 in comparison group; $p=$ 0.59). There was no significant difference between the comparison group and the treatment group in terms of multiple fractures at baseline, especially among those with more than three fractures at baseline.

The risk of a secondary VCF is shown in Fig. 2. The proportion of patients in the treatment group with confirmed

subsequent VCFs at 90 days post-index fracture had almost five times the risk of the comparison group (omitting progressive fractures) and over three times that of the comparison group when including progressive VCFs. At 360 days post index, approximately 19% of treatment patients had a subsequent VCF compared to just fewer than 7% of the comparison group. This latter proportion increased to 10% if progressive VCFs at the same level were included. The median time to fracture in the treatment group was within 2 months of the vertebroplasty/kyphoplasty procedure, compared to over 3 months in the comparison group (median days to subsequent fracture=47; inter-quartile range (IQR) 22–71 vs. 106; IQR 61–154, $p=$NS; data not shown). The number of physician visits within 360 days post the index date varied significantly between the treatment (14.0± 14.0) and comparison groups (25.2±23.7, $p<0.01$; data not shown). Cement leakage was identified as an immediate adverse event of 19% ($n=9$) of the treatment patients and did not differ by type of procedure. Four (8%) of the 48 patients had a vertebroplasty or kyphoplasty performed concurrently at more than one spinal level.

Table 2 shows the rates and odds of secondary VCFs stratified by time (either 90 or 360 days post index) and by subsequent fracture location. Treatment group patients were significantly more likely than comparison group patients to have a subsequent VCF, even after accounting for the important co-factors of osteoporosis diagnosis before the index date, number of comorbidities, and age. This effect was particularly noticeable within 90 days and remained the same in magnitude after multivariate adjustment [odds ratio (OR)=6.8; 95% confidence interval (CI) 1.7–26.9]. Most of the secondary fractures in the treatment group occurred within 90 days (78%) compared to less than half of the secondary fractures in the comparison group, even when including the progressive fractures. In both groups, the odds of experiencing additional adjacent-level fractures was significantly increased, particularly within 90 days, and almost all subsequent fractures occurred within three levels of the index vertebra. The odds of a subsequent fracture in the treatment group vs. the comparison group when including progressive fractures were similar to the primary analysis at 90 days (OR=4.6; 95% CI 1.4–15.5; data not shown). In sensitivity analyses examining relationships within 90 days post-index date, secondary VCFs non-significantly trended toward being more common among treatment patients when compared to comparison group patients that were hospitalized with their index fractures (48 in treatment group and 37 in comparison group; adjusted OR=6.0; 95% CI 0.8–44.1). In addition, among patients with index fractures characterized as new in both groups (26 in treatment group and 63 in comparison group), we saw a similar non-significant trend (adjusted OR=4.8, 95% CI 0.9–26.9).
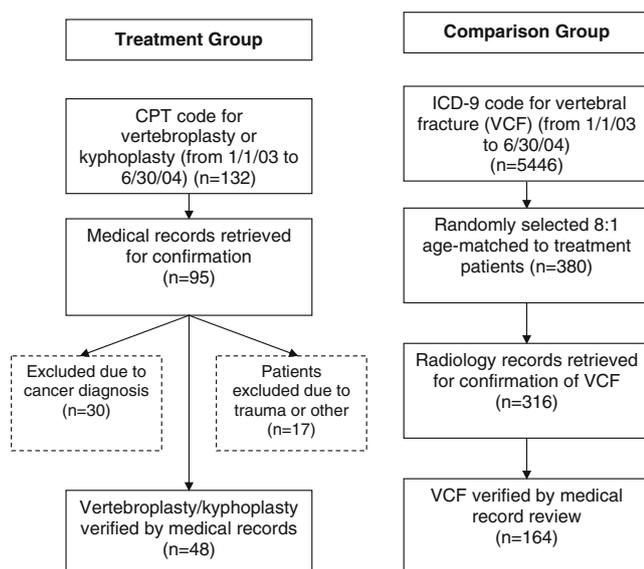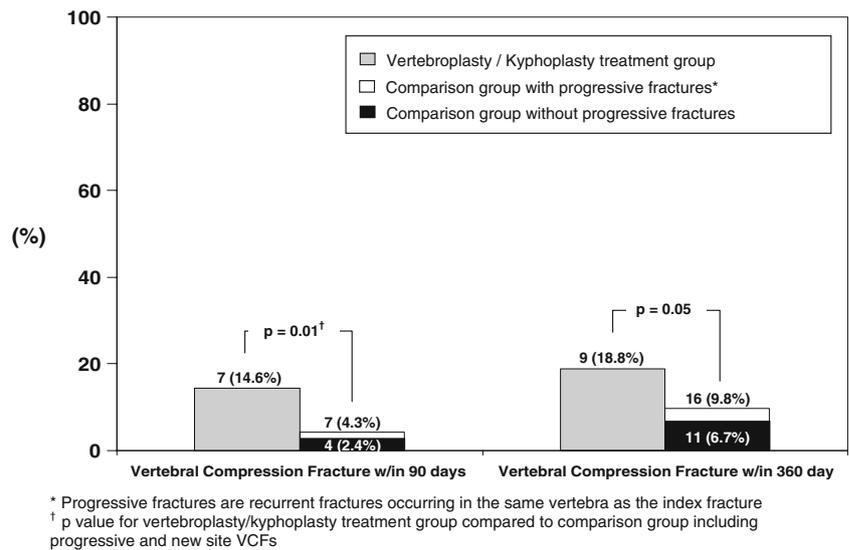

Fig. 1 Summary diagram of selection of vertebroplasty/kyphoplasty treatment and comparison groups

Fig. 2 Proportion of vertebro-plasty/kyphoplasty treatment (*n*=48) and comparison (*n*=164) group patients with secondary fractures

Legend:
- Vertebroplasty / Kyphoplasty treatment group
- Comparison group with progressive fractures*
- Comparison group without progressive fractures

p = 0.01†   p = 0.05

7 (14.6%)   9 (18.8%)
7 (4.3%)   16 (9.8%)
4 (2.4%)   11 (6.7%)

Vertebral Compression Fracture w/in 90 days   Vertebral Compression Fracture w/in 360 day

(%)

* Progressive fractures are recurrent fractures occurring in the same vertebra as the index fracture
† p value for vertebroplasty/kyphoplasty treatment group compared to comparison group including progressive and new site VCFs

Discussion

Vertebroplasty and kyphoplasty procedures were developed to improve short-term outcomes from painful vertebral fractures [8, 9], but the long-term safety of these procedures is still unknown. In comparison to a group of patients not undergoing vertebroplasty/kyphoplasty, our retrospective cohort study identified a significant increased risk of subsequent vertebral fractures among patients treated with these procedures for non-traumatic, non-cancer-related VCFs, especially within 3 months of the procedure. As predicted from biomechanical studies [5, 6, 10], fractures at adjacent levels were also more likely to occur in the treatment group.

To our knowledge, no prior studies of vertebroplasty or kyphoplasty outcomes have included a population-based comparison group. The majority of vertebroplasty evidence consists of primarily retrospective, single-center studies, which lack a control group [11]. Two non-randomized prospective studies comparing vertebroplasty to conservative treatment, recruited from those patients who refused a vertebroplasty procedure, found little difference in longer-term outcomes or subsequent fractures [12, 13]. These studies had relatively short follow-up and contained small control groups. In contrast, another prospective study comparing those treated with kyphoplasty to a small comparison group of those who declined the procedure showed a decrease in pain scores and subsequent vertebral fractures in the treatment group [14].

Previous uncontrolled prospective studies of vertebroplasty procedures conducted at a single facility have shown that the rate of subsequent incident VCF among patients treated with vertebroplasty ranges from 18% to 36% within 1 year [15–19]. Similarly, retrospective single-center studies have found subsequent fracture rates among vertebroplasty [20–22] and kyphoplasty [23, 24] patients of 12% to 26%. Our controlled study based in a regional private insurance population showed a 1-year rate of secondary VCF of 18.8% among treated patients compared to the control-group rate of 9.7%. The timing of post-vertebroplasty VCFs in our study also is consistent with prior vertebroplasty studies, which have shown that between 43% and 67% of subsequent incident fractures occur within 3 months of the treatment procedure [22, 25, 26]. The fracture rate in our comparison group was similar

Table 2 Rates, crude, and adjusted odds of secondary vertebral compression fractures (VCFs; does not include progression of existing vertebral fractures in the comparison group) by time period and fracture location for vertebroplasty/kyphoplasty (treatment) and comparison groups

	Treatment, *n* (%)	Comparison, *n* (%)	Unadjusted odds (95% CI)	Adjusted odds (95% CI)[a]
Within 90 days post index[b]				
Any secondary VCF	7 (14.6%)	4 (2.4%)	6.8 (1.9–24.5)	6.8 (1.7–26.9)
Adjacent fracture within 1 vertebra	4 (8.3%)	3 (1.8%)	4.9 (1.1–22.6)	4.2 (0.9–20.3)
Within 360 days post index				
Any secondary VCF	9 (18.8%)	11 (6.7%)	3.2 (1.2–8.3)	2.9 (1.1–7.9)
Adjacent fracture within 1 vertebra	4 (8.3%)	6 (3.7%)	2.4 (0.6–8.9)	2.0 (0.5–7.6)

[a] Multivariable logistic regression analysis adjusted for osteoporosis diagnosis before index, number of comorbidities, sex, and age
[b] Index = Incident vertebroplasty/kyphoplasty procedure for a treatment patient; incident VCF diagnosis for a comparison patient

to randomized controlled trial fracture rates among control-group patients with at least two prior VCFs [27] and at least one VCF or low bone mineral density measurements (T score<−2.5 at femoral neck or lumbar spine) [28, 29]. Several studies suggest that patients are at a higher risk for adjacent-level fractures following a vertebroplasty [15, 26], especially during the first 3 months [22, 23, 26]. In our study, the odds of an adjacent-level fracture following the vertebroplasty or kyphoplasty procedure when comparing treatment patients to comparison patients showed an approximate four-fold increase within 90 days and a two-fold increase within 360 days.

Cement leakage, the most common complication of vertebroplasty and kyphoplasty procedures, may occur more often than clinically detected [30, 31], and it is thought this may increase the possibility of adjacent fractures [32]. In our study, although approximately 19% of treated patients had mention of this occurrence in the procedural records, we were underpowered to explore a possible relationship.

Despite the large size and good generalizability of the health plan we examined, there were a relatively small number of vertebroplasty and kyphoplasty procedures performed during our study time period. This was partially based on strict exclusion and validation criteria for patients receiving care in this health plan. The small number of secondary fracture outcomes and inconsistently reported information in medical records (i.e., osteoporosis medications) limited potential subgroup analyses and the number of co-variates we could control for as potential confounders of the relationship between treatment exposure and fractures, thereby increasing the chance of residual confounding. As with all retrospective studies, there is always the likelihood that other factors, not measured in our study, could be the reason for the differences observed. We were not able to collect information on medication use, specifically bisphosphonates and other anti-osteoporotic medications, due to the lack of administrative pharmacy data and the inconsistent and incomplete documentation of medication use in the reviewed medical records, predominately from surgeons and radiologists. This limited our ability to control for these potential confounders. However, our ability to control for age, sex, osteoporosis diagnosis, and comorbidity and the fact that the magnitude of our estimates remained the same after adjustments were made add to the strength of our findings. Examining subsets of patients with new baseline fractures and only comparison group patients requiring hospitalizations for their VCFs further adjusted for possible case mix variations. Although the magnitude of the treatment effect was attenuated, the trend toward increased fracture risk with vertebroplasty/kyphoplasty persisted in these under-powered sensitivity analyses. Additionally, our study was underpowered to specifically examine specific differences between kyphoplasty and vertebroplasty.

As with any study using administrative data, one limitation may be misclassification of patients due to coding errors and interpretation. In an effort to minimize misclassification of outcomes, we established stringent study inclusion criteria, including only validated fractures confirmed by review of medical records. We found that 60% of treatment patients who did not have evidence of cancer either in the claims data or medical records still had received a diagnosis claim for a pathologic vertebral fracture (CPT-4 code: 733.13) in the administrative data. Therefore, since medical record confirmation was required of all patients, we included those with a pathologic fracture code in the comparison group as well. It is possible, due to varying quality of records received, that some patients may have been misclassified as to the indication for their fracture and subsequent fracture status; however, it is unlikely that differential misclassification occurred between treatment or comparison groups. In our study, we were not able to retrieve the actual radiographic images but were limited to the radiology reports. Therefore, we were not able to fully determine qualitative differences or level of collapse in specific baseline fractures, but we did ascertain a measure of fracture quantity, the number of baseline fractures present in the comparison and treatment groups.

Another potential limitation of all retrospective cohort studies is the possibility of diagnostic detection bias (differential outcome ascertainment). Specifically, it is possible that patients who had a vertebroplasty or kypho-plasty procedure were more likely to be followed more closely by their physician and have additional radiographic procedures documented. Yet, in our study, the comparison group had a similar mean number of physician visits in the 180 days prior to the index event, but a significantly higher mean number of physician visits than the treatment group within the year following the index event. The reason for this difference is not clear but would seem to only increase the possibility of detecting new fractures in the comparison group, thereby biasing toward the null hypothesis. An additional concern is the difficulty of diagnosing vertebral fractures solely through review of spinal imaging studies performed for clinical and not research purposes. While multiple types of radiologic testing (magnetic resonance imagery, computerized tomography, and/or bone scans) were reviewed in both groups where available, it is possible that some vertebral fractures were not recorded by radiologists and not included in the radiology reports that we reviewed. Since the majority of vertebral fractures are asymptomatic and do not necessarily trigger additional radiologic follow-up, it is difficult to determine how this limitation affects our study, but it would seem to affect both groups equally and bias results toward the null hypothesis.

Although vertebroplasty and kyphoplasty procedures have been shown to be efficacious for short-term pain relief, our

finding of an increased risk of subsequent fractures in a controlled population-based study of insured patients raises concern about their short- to moderate-term safety. Although randomized controlled clinical trials to further study the long-term impact of these procedures are clearly needed to better define their place in the osteoporosis treatment armamentarium, challenges in recruitment to such trials [2] lead to an important role of carefully conducted observational studies to address timely questions of clinical relevance.

Conflicts of interest Ms. Mudano and Dr. Briggs are currently employed with Blue Cross Blue Shield of Alabama. Dr. Curtis receives research support from Merck, Novartis, Amgen, and Lilly, is a consultant for Roche, and has honoraria from Merck, Proctor & Gamble, Lilly and Roche. Dr. Saag receives consulting fees and research support from Merck, Novartis, Roche, Proctor & Gamble, Amgen, and Lilly and is a consultant for Glaxo Smith Kline. All other authors stated that they had no conflicts of interest.

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Appendix

Table 3 Diagnostic and procedure codes used for identification and exclusions of vertebroplasty/kyphoplasty treatment and comparison groups

Description of codes	Codes used in the study
CPT codes used for vertebroplasty/kyphoplasty identification	22520, 22521, 22522, 76012, 76013
CPT codes for spinal radiology	72xxx[a], 78306
HCPCS codes used for vertebroplasty/kyphoplasty identification	S2360, S2361, S2362, S2363
ICD-9 codes for identifying vertebral fractures	805.2, 805.4, 805.8, 733.13
ICD-9 codes used to exclude treatment and comparison patients (includes codes for malignant neoplasms, non-specific hemangiomas, bone and plasma cell neoplasms)	140.xx to 208.xx, 228.09, 238.0, 238.6, 239.2

CPT Current Procedural Terminology, *ICD-9* International Classification of Diseases, Ninth Revision, *HCPCS* Healthcare Common Procedure Coding System

[a] Refers to all subsequent modifiers to the parent code

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