

Risk of Osteoporotic Fracture After Steroid Injections in Patients With Medicare

Leah Y. Carreon, MD, MSc, Kevin L. Ong, PhD, Edmund Lau, MS, Steven M. Kurtz, PhD, and Steven D. Glassman, MD

Abstract

To further evaluate the relationship between steroid injections and osteoporotic fracture risk, we analyzed Medicare administrative claims data on both large-joint steroid injections (LJSIs) into knee and hip and transforaminal steroid injections (TSIs), as well as osteoporotic hip and wrist fractures. Our hypothesis was that a systemic effect of steroid injections would increase fracture risk in all skeletal locations regardless of injection site, whereas a local effect would produce a disproportionate increased risk of spine fracture with spine injection.

Patients treated with an LSJI, a TSI, or an

epidural steroid injection (ESI) were identified from 5% Medicare claims data. Patients under age 65 years and patients with prior osteoporotic fracture were excluded. Analyses were performed to determine fracture risk (adjusted hazard ratio) for each type of injection.

Analysis of the Medicare data revealed that ESIs were associated with decreased osteoporotic spine fracture risk, but the effect was small and might not be clinically relevant. ESIs did not influence osteoporotic hip or wrist fracture risk, but LJSIs reduced the risk.

Epidural steroid injections (ESIs) are widely used in the nonoperative treatment of low back pain, radicular leg pain, and spinal stenosis. The treatment rationale is that locally injected anti-inflammatory drugs, such as steroids, reduce inflammation by inhibiting formation and release of inflammatory cytokines, leading to pain reduction.^{1,2} According to 4 systematic reviews, the best available evidence of the efficacy of ESIs is less than robust.³⁻⁶ These reviews were limited by the heterogeneity of patient selection, delivery mode, type and dose of steroid used, number and frequency of ESIs, and outcome measures.

The association of chronic oral steroid use and the development of osteoporosis was previously established.^{7,8} One concern is that acute exposure to steroids in the form of lumbar ESIs may also lead to osteoporosis and then a pathologic fracture of the vertebra. Several studies have found no association between bone mineral density and cu-

mulative steroid dose,^{9,10} mean number of ESIs, or duration of ESIs,¹⁰ though other studies have found

Take-Home Points

- Analysis of patients in the Medicare database showed that each successive ESI decreased the risk of an osteoporotic spine fracture by 2%, and that each successive LSJI decreases it by 4%.
- Although statistically significant, this may not be clinically relevant.
- Successive ESI did not influence the risk of developing an osteoporotic hip or wrist fracture, but that each additional LSJI reduced the risk.
- Prolonged steroid exposure was found to increase the risk of spine fracture for ESI and LSJI patients.
- Acute exposure to exogenous steroids via the epidural space, transforaminal space, or large joints does not seem to increase the risk of an osteoporotic fracture of the spine, hip, or wrist.

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lower bone mineral density in postmenopausal women treated with ESIs.¹¹⁻¹³

In a study of 3000 ESI patients propensity-matched to a non-ESI cohort, Mandel and colleagues¹⁴ found that each successive ESI increased the risk of osteoporotic spine fracture by 21%. This clinically relevant 21% increased risk might lead physicians to stop prescribing or using this intervention. However, the association between osteoporotic fractures and other types of steroid injections remains poorly understood and underinvestigated.

To further evaluate the relationship between steroid injections and osteoporotic fracture risk, we analyzed Medicare administrative claims data on both large-joint steroid injections (LJSIs) into knee and hip and transforaminal steroid injections (TSIs), as well as osteoporotic hip and wrist fractures. Our hypothesis was that a systemic effect of steroid injections would increase fracture risk in all skeletal locations regardless of injection site, whereas a local effect would produce a disproportionate increased risk of spine fracture with spine injection.

Materials and Methods

Medicare is a publicly funded US health insurance program for people 65 years old or older, people under age 65 years with certain disabilities, and people (any age) with end-stage renal disease or amyotrophic lateral sclerosis. The 5% Medicare Part B (physician, carrier) dataset contains individual claims records for a random sample of Medicare beneficiaries (~2.4 million enrollees). Patients who received steroid injections were identified from 5% Medicare claims made between January 1, 2004 and December 31, 2011. LJSIs were identified by *Current Procedural Terminology (CPT)* code 20610 and any of 16 other *CPT* codes: J0702, J1020, J1030, J1040, J1094, J1100, J1700, J1710, J1720, J2650, J2920, J2930, J3300, J3301, J3302, and J3303. ESIs were identified by *CPT* code 62310, 62311, 62318, or 62319, and TSIs by *CPT* code 64479, 64480, 64483, or 64484. Patients were followed in their initial injection cohort. For example, a patient who received an ESI initially and later received an LJSI remained in the ESI cohort.

Several groups of patients were excluded from the study: those who received Medicare coverage because of their age (under 65 years) and disabilities; those who received Medicare health benefits through health maintenance organizations (healthcare expenses were not submitted to the Centers for Medicare & Medicaid Services for payment,

and therefore claims were not in the database or were incomplete); those with a prior claim history of <12 months (incomplete comorbidity history); and those who received a diagnosis of osteoporotic fracture (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* code 733.1x) before the initial steroid injection.

We determined the incidence of osteoporotic wrist, hip, and spine fractures within 1, 2, and 8 years after LJSI, ESI, and TSI. Wrist, hip, and spine fractures were identified by *ICD-9-CM* diagnosis codes 733.12, 733.13, and 733.14, respectively. We also determined the number of steroid injections given before wrist, hip, or spine fracture or, if no fracture occurred, before death or the end of the data period.

Statistical Analysis

Multivariate Cox regression analysis was performed to evaluate the risk factors for wrist, spine, and hip fractures. The covariates in this model included age, sex, race, census region, Medicare buy-in status, Charlson Comorbidity Index (CCI),¹⁵ year, and number of steroid injections before fracture, death, or end of data period. Medicare buy-in status, which indicates whether the beneficiary received financial assistance in paying insurance premiums, was used as a proxy for socioeconomic status. CCI is used as a composite score of a patient's general health status in terms of comorbidities.^{15,16} Four previously established categories¹⁷ were used to group CCIs in this study: 0 (none), 1 to 2 (low), 3 to 4 (moderate), and 5 or more (high). In addition, several diagnoses made within the 12 months before initial steroid injection were considered: osteoporosis (*ICD-9-CM* codes 733.0x, V82.81), Cushing syndrome (*ICD-9-CM* code 255.0), long-term (current) use of bisphosphonates (*ICD-9-CM* code V58.68), asymptomatic postmenopausal status (*ICD-9-CM* code V49.81), postmenopausal hormone replacement therapy (*ICD-9-CM* code V07.4), and long-term (current) use of steroids (*ICD-9-CM* code V58.65). The comparison of relative risk between any groups was reported as the adjusted hazard ratio (AHR), which is the ratio of the hazard rates of that particular outcome, taking into account inherent patient characteristics such as age, sex, and race as covariates. AHR of 1 corresponds to equivalent risk, AHR of >1 to elevated risk, and AHR of <1 to reduced risk.

Results

Using the 5% Medicare data for 2004 to 2011, we identified 275,999 Medicare beneficiaries who

underwent LJSI, 93,943 who underwent ESI, and 32,311 who underwent TSI. During this period, TSI use increased, ESI use decreased, and LJSI use was relatively stable (Figure). LJSI patients underwent a mean (SD) of 3.0 (4.1) LJSIs; ESI patients, 3.2 (3.9) ESIs; and TSI patients, 7.5 (12.1) TSIs. Very few patients had more than 1 steroid injection site (Table 1).

The risk for osteoporotic spine fracture 1, 2, and 8 years after ESI, TSI, or LJSI was affected by age, race, sex, and CCI ($P < .001$ for all; Tables 2-4). Patients with higher CCIs, females, older patients, and white patients had higher spine fracture risks. For ESI and LJSI patients, long-term steroid use was also associated with higher spine fracture risk at all examined time points. For example, 8 years after ESI and LJSI, patients with long-term steroid use had 88% ($P = .002$) and 47% ($P = .008$) elevated risk of spine fracture, respectively. For TSI patients, spine fracture risk tended to be higher in patients with long-term steroid use 1 and 2 years after injection; this association was significant 8 years after injection ($P = .046$). ESI patients of lower socioeconomic status (Medicare buy-in) also had higher spine fracture risk at all examined time points, whereas LJSI and TSI patients did not. Two years after injection, each additional ESI decreased the relative risk of spine fracture by 2% ($P < .001$), each additional TSI decreased it by 1% ($P = .009$), and each additional LJSI decreased it by 4% ($P < .001$).

The risk for osteoporotic hip fracture after 1 and 2 years was affected by age and number of LJSIs and TSIs but not by number of ESIs. Sex and CCI were also risk factors for hip fracture at 1 and 2 years for ESI and LJSI patients, as was race for LJSI patients. Risk for osteoporotic wrist fracture at 1 and 2 years was affected by sex and race for ESI and LJSI patients; age, race, CCI, and long-

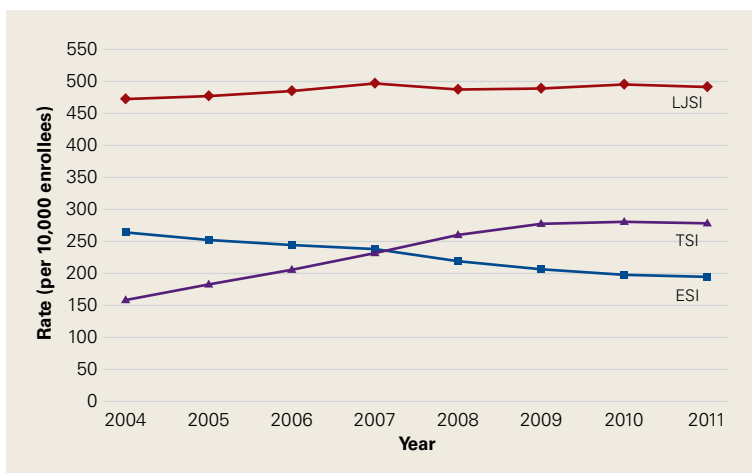


Figure. Between 2004 and 2011, use of transforaminal steroid injection (TSI) increased, use of epidural steroid injection (ESI) decreased, and use of large-joint steroid injection (LJSI) was relatively stable.

term steroid use were risk factors for TSI patients at all time points. Higher number of LJSIs, but not ESIs or TSIs, was associated with lower wrist fracture risk.

Discussion

ESIs continue to be used in the nonoperative treatment of low back pain, radicular leg pain, and spinal stenosis. Although the present study found ESI use increased in the Medicare population between 1994 and 2001,¹⁸ the trend is reversing, decreasing by 25%, with rates of 264 per 10,000 Medicare enrollees in 2004 and 194 per 10,000 enrollees in 2011. ESI use may have changed after systematic reviews revealed there was no clear evidence of the efficacy of ESIs in managing low back pain and radicular leg pain^{3,5,6} or spinal stenosis.⁴

Nevertheless, ESIs are widely used because of the perceived benefit balanced against the perceived rarity of adverse events.⁶ Even if patients recognize a low likelihood of significant benefit,

Table 1. Number of Steroid Injections Before Fracture or, If No Fracture, Before Death or End of Data Period

Patient Group	Injection Type							
	Large Joint		Epidural		Transforaminal		Any	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
LJSI	3.0 (4.1)	2 (1-3)	0.4 (1.6)	0 (0-0)	0.4 (3.2)	0 (0-0)	3.8 (5.9)	2 (1-4)
ESI	0.7 (2.3)	0 (0-0)	3.2 (3.9)	2 (1-4)	0.9 (4.6)	0 (0-0)	4.8 (7.3)	3 (1-6)
TSI	0.7 (2.2)	0 (0-0)	0.8 (2.3)	0 (0-0)	7.5 (12.1)	4 (2-9)	9.1 (13.1)	6 (3-11)

Abbreviations: ESI, epidural steroid injection; IQR, interquartile range; LJSI, large-joint steroid injection; SD, standard deviation; TSI, transforaminal steroid injection.

Table 2. Spine, Hip, and Wrist Adjusted Relative Fracture Risk (95% Confidence Interval) for Patients Who Received Epidural Steroid Injections Within 1, 2, and 8 Years^a

Factor	Patient Group Comparison	Fracture Type								
		Spine			Hip			Wrist		
		1 Year	2 Years	8 Years	1 Year	2 Years	8 Years	1 Year	2 Years	8 Years
Age, y	70-74 vs 65-69	1.31 (1.20-1.42)	1.31 (1.20-1.42)	1.31 (1.20-1.43)	1.39 (1.01-1.90)	1.39 (1.02-1.91)	1.39 (1.02-1.91)	0.82 (0.44-1.52)	0.82 (0.44-1.52)	0.82 (0.44-1.53)
	75-79 vs 65-69	1.66 (1.53-1.80)	1.67 (1.54-1.81)	1.70 (1.57-1.85)	1.32 (0.95-1.83)	1.33 (0.96-1.84)	1.36 (0.98-1.89)	0.79 (0.43-1.46)	0.80 (0.44-1.47)	0.82 (0.45-1.50)
	80-84 vs 65-69	2.03 (1.86-2.22)	2.06 (1.89-2.25)	2.16 (1.98-2.36)	1.74 (1.24-2.44)	1.76 (1.26-2.47)	1.87 (1.33-2.62)	1.15 (0.63-2.11)	1.16 (0.64-2.13)	1.22 (0.67-2.24)
	85+ vs 65-69	2.58 (2.35-2.83)	2.70 (2.46-2.96)	2.96 (2.70-3.25)	1.86 (1.27-2.73)	1.95 (1.33-2.86)	2.19 (1.49-3.22)	1.26 (0.60-2.64)	1.31 (0.63-2.75)	1.45 (0.69-3.04)
Sex	Female vs male	1.58 (1.48-1.68)	1.57 (1.47-1.67)	1.55 (1.45-1.65)	1.69 (1.34-2.12)	1.68 (1.33-2.11)	1.65 (1.31-2.07)	4.27 (2.22-8.22)	4.26 (2.21-8.18)	4.19 (2.18-8.07)
Race	Asian vs white	0.60 (0.44-0.81)	0.59 (0.44-0.79)	0.58 (0.43-0.79)	0.17 (0.02-1.29)	0.17 (0.02-1.27)	0.16 (0.02-1.24)	1.04 (0.11-9.49)	1.02 (0.11-9.38)	1.01 (0.11-9.29)
	Black vs white	0.23 (0.19-0.29)	0.23 (0.19-0.29)	0.23 (0.18-0.29)	0.51 (0.27-0.97)	0.51 (0.27-0.96)	0.50 (0.26-0.94)	0.70 (0.22-2.27)	0.69 (0.21-2.25)	0.69 (0.21-2.23)
	Hispanic vs white	0.64 (0.49-0.84)	0.64 (0.49-0.84)	0.62 (0.47-0.81)	0.53 (0.18-1.61)	0.53 (0.18-1.60)	0.51 (0.17-1.53)	2.12 (0.48-9.40)	2.11 (0.48-9.29)	2.03 (0.46-8.90)
	Other/unknown vs white	0.71 (0.52-0.98)	0.70 (0.51-0.96)	0.69 (0.50-0.94)	0.73 (0.25-2.19)	0.71 (0.24-2.13)	0.70 (0.24-2.10)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Charlson Comorbidity Index	1-2 vs 0	1.16 (1.08-1.24)	1.17 (1.09-1.25)	1.20 (1.12-1.29)	1.15 (0.86-1.54)	1.16 (0.87-1.55)	1.20 (0.90-1.60)	1.03 (0.62-1.69)	1.04 (0.63-1.71)	1.06 (0.64-1.75)
	3-4 vs 0	1.29 (1.19-1.39)	1.32 (1.22-1.43)	1.40 (1.29-1.51)	1.29 (0.95-1.75)	1.32 (0.98-1.80)	1.42 (1.05-1.93)	1.13 (0.62-2.06)	1.16 (0.64-2.12)	1.23 (0.68-2.25)
	5+ vs 0	1.39 (1.26-1.53)	1.48 (1.34-1.64)	1.63 (1.48-1.80)	2.52 (1.81-3.49)	2.71 (1.96-3.75)	3.05 (2.20-4.22)	0.71 (0.29-1.71)	0.76 (0.31-1.84)	0.84 (0.35-2.04)
Medicare buy-in	Yes vs no	1.13 (1.03-1.24)	1.15 (1.05-1.26)	1.17 (1.07-1.29)	1.40 (1.00-1.96)	1.42 (1.02-1.99)	1.46 (1.04-2.04)	0.85 (0.38-1.90)	0.86 (0.38-1.93)	0.87 (0.39-1.97)
Cushing syndrome diagnosis	Yes vs no	1.62 (0.73-3.56)	1.61 (0.73-3.55)	1.69 (0.75-3.80)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	4.25 (1.93->20)	15.36 (2.06->20)	16.24 (2.20->20)
Hormone replacement therapy	Yes vs no	0.80 (0.54-1.18)	0.80 (0.54-1.17)	0.78 (0.53-1.15)	1.12 (0.28-4.55)	1.12 (0.28-4.55)	1.08 (0.27-4.41)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Osteoporosis diagnosis	Yes vs no	1.86 (1.75-1.99)	1.87 (1.75-1.99)	1.87 (1.75-1.99)	1.39 (1.06-1.81)	1.39 (1.06-1.81)	1.39 (1.06-1.81)	1.56 (0.96-2.53)	1.56 (0.96-2.53)	1.57 (0.97-2.54)
Long-term steroid use	Yes vs no	1.86 (1.25-2.76)	1.87 (1.25-2.78)	1.88 (1.27-2.80)	2.36 (0.58-9.61)	2.36 (0.58-9.60)	2.51 (0.62-10.26)	5.34 (0.72->20)	5.28 (0.71->20)	5.42 (0.73->20)
Injections, n	—	0.98 (0.97-0.99)	0.98 (0.97-0.98)	0.97 (0.97-0.98)	0.98 (0.95-1.00)	0.97 (0.95-1.00)	0.97 (0.94-1.00)	0.99 (0.95-1.04)	0.99 (0.95-1.04)	0.99 (0.95-1.04)

^aRed values, $P < .01$; blue values, $P < .001$.

Table 3. Spine, Hip, and Wrist Adjusted Relative Fracture Risk (95% Confidence Interval) for Patients Who Received Transforaminal Steroid Injections Within 1, 2, and 8 Years^a

Factor	Patient Group Comparison	Fracture Type								
		Spine			Hip			Wrist		
		1 Year	2 Years	8 Years	1 Year	2 Years	8 Years	1 Year	2 Years	8 Years
Age, y	70-74 vs 65-69	1.15 (0.98-1.34)	1.15 (0.98-1.34)	1.15 (0.98-1.34)	0.82 (0.36-1.88)	0.82 (0.36-1.88)	0.82 (0.36-1.89)	1.21 (0.07-19.70)	1.21 (0.08-19.53)	1.21 (0.07-19.55)
	75-79 vs 65-69	1.70 (1.47-1.96)	1.72 (1.49-1.98)	1.74 (1.51-2.01)	1.19 (0.56-2.55)	1.21 (0.56-2.58)	1.23 (0.57-2.62)	10.66 (1.28->20)	10.77 (1.30->20)	11.05 (1.34->20)
	80-84 vs 65-69	1.93 (1.65-2.25)	1.96 (1.68-2.29)	2.05 (1.76-2.39)	2.24 (1.15-4.39)	2.29 (1.17-4.48)	2.40 (1.22-4.70)	12.68 (1.61->20)	12.87 (1.64->20)	13.31 (1.67->20)
	85+ vs 65-69	2.23 (1.88-2.64)	2.32 (1.96-2.76)	2.56 (2.16-3.04)	3.62 (1.74-7.54)	3.82 (1.83-7.98)	4.23 (2.01-8.93)	3.31 (0.20->20)	3.44 (0.20->20)	3.90 (0.23->20)
Sex	Female vs male	1.57 (1.41-1.76)	1.57 (1.40-1.76)	1.55 (1.39-1.74)	1.54 (0.89-2.69)	1.53 (0.88-2.67)	1.51 (0.87-2.62)	1.68 (0.44-6.46)	1.67 (0.44-6.38)	1.59 (0.42-6.06)
Race	Asian vs white	0.72 (0.48-1.06)	0.72 (0.48-1.07)	0.70 (0.47-1.05)	1.97 (0.73-5.35)	1.98 (0.73-5.37)	1.93 (0.72-5.17)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	Black vs white	0.32 (0.22-0.46)	0.32 (0.22-0.46)	0.32 (0.22-0.45)	0.64 (0.16-2.59)	0.63 (0.16-2.54)	0.63 (0.16-2.49)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	Hispanic vs white	0.78 (0.53-1.16)	0.77 (0.52-1.14)	0.74 (0.50-1.11)	2.34 (0.44-12.44)	2.27 (0.42-12.19)	2.21 (0.41-11.86)	1.43 (0.10-19.72)	1.43 (0.10->20)	1.25 (0.08-19.02)
	Other/unknown vs white	0.79 (0.52-1.22)	0.78 (0.51-1.19)	0.77 (0.50-1.18)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Charlson Comorbidity Index	1-2 vs 0	1.20 (1.07-1.35)	1.21 (1.07-1.36)	1.24 (1.10-1.40)	1.92 (1.11-3.32)	1.93 (1.11-3.34)	1.99 (1.15-3.45)	0.74 (0.26-2.10)	0.75 (0.27-2.12)	0.78 (0.27-2.24)
	3-4 vs 0	1.34 (1.16-1.54)	1.36 (1.17-1.57)	1.43 (1.24-1.66)	1.82 (0.88-3.78)	1.86 (0.90-3.86)	1.99 (0.95-4.13)	0.92 (0.26-3.21)	0.94 (0.27-3.29)	0.98 (0.28-3.42)
	5+ vs 0	1.88 (1.56-2.27)	1.99 (1.66-2.40)	2.19 (1.82-2.64)	2.10 (0.83-5.30)	2.27 (0.90-5.73)	2.55 (1.01-6.42)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Medicare buy-in	Yes vs no	0.90 (0.74-1.10)	0.90 (0.74-1.10)	0.90 (0.73-1.11)	0.56 (0.23-1.39)	0.56 (0.22-1.40)	0.56 (0.22-1.40)	3.28 (0.75-14.29)	3.26 (0.75-14.29)	3.11 (0.70-13.81)
Cushing syndrome diagnosis	Yes vs no	1.12 (0.29-4.36)	1.06 (0.28-4.02)	1.03 (0.28-3.82)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Hormone replacement therapy	Yes vs no	0.34 (0.11-1.04)	0.35 (0.11-1.05)	0.34 (0.11-1.02)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Osteoporosis diagnosis	Yes vs no	1.60 (1.41-1.81)	1.61 (1.42-1.82)	1.62 (1.43-1.83)	1.98 (1.20-3.28)	1.99 (1.20-3.30)	2.01 (1.22-3.33)	3.53 (1.30-9.57)	3.54 (1.30-9.63)	3.58 (1.32-9.72)
Long-term steroid use	Yes vs no	1.96 (0.95-4.05)	2.06 (0.99-4.27)	2.10 (1.01-4.34)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Injections, n	—	0.99 (0.98-1.00)	0.99 (0.98-1.00)	0.99 (0.98-1.00)	0.95 (0.92-0.99)	0.95 (0.91-0.99)	0.95 (0.91-0.99)	1.00 (0.98-1.03)	1.00 (0.98-1.03)	1.00 (0.97-1.03)

^aRed values, $P < .01$; blue values, $P < .001$.

Table 4. Spine, Hip, and Wrist Adjusted Relative Fracture Risk (95% Confidence Interval) for Patients Who Received Large-Joint Steroid Injections Within 1, 2, and 8 Years^a

Factor	Patient Group Comparison	Fracture Type								
		Spine			Hip			Wrist		
		1 Year	2 Years	8 Years	1 Year	2 Years	8 Years	1 Year	2 Years	8 Years
Age, y	70-74 vs 65-69	1.26 (1.19-1.34)	1.27 (1.19-1.35)	1.27 (1.19-1.35)	1.34 (1.05-1.71)	1.34 (1.05-1.71)	1.34 (1.05-1.71)	0.82 (0.47-1.42)	0.82 (0.47-1.42)	0.82 (0.47-1.43)
	75-79 vs 65-69	1.76 (1.66-1.87)	1.78 (1.67-1.88)	1.82 (1.71-1.93)	1.75 (1.38-2.21)	1.76 (1.40-2.22)	1.81 (1.43-2.28)	0.94 (0.60-1.47)	0.95 (0.60-1.48)	0.97 (0.62-1.51)
	80-84 vs 65-69	2.13 (2.01-2.26)	2.19 (2.06-2.31)	2.33 (2.20-2.47)	2.29 (1.82-2.88)	2.34 (1.86-2.94)	2.51 (2.00-3.16)	0.95 (0.58-1.54)	0.97 (0.60-1.57)	1.03 (0.64-1.67)
	85+ vs 65-69	2.30 (2.16-2.46)	2.45 (2.30-2.61)	2.81 (2.64-2.99)	2.92 (2.27-3.76)	3.10 (2.41-3.99)	3.61 (2.80-4.64)	1.37 (0.81-2.31)	1.45 (0.86-2.45)	1.66 (0.99-2.80)
Sex	Female vs male	1.73 (1.65-1.81)	1.72 (1.64-1.80)	1.70 (1.62-1.78)	1.44 (1.22 – 1.71)	1.43 (1.21-1.70)	1.40 (1.18-1.66)	3.78 (2.24-6.36)	3.76 (2.23-6.33)	3.70 (2.19-6.25)
	Race	Asian vs white	0.84 (0.72-0.99)	0.83 (0.71-0.97)	0.79 (0.68-0.93)	0.51 (0.23-1.11)	0.50 (0.23-1.09)	0.48 (0.22-1.04)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Race	Black vs white	0.30 (0.26-0.35)	0.30 (0.26-0.35)	0.30 (0.26-0.35)	0.59 (0.40-0.87)	0.59 (0.40-0.87)	0.58 (0.39-0.86)	0.31 (0.10-0.94)	0.31 (0.10-0.94)	0.31 (0.10-0.93)
	Hispanic vs white	0.74 (0.59-0.92)	0.72 (0.57-0.91)	0.69 (0.55-0.87)	0.70 (0.36-1.35)	0.68 (0.35-1.33)	0.65 (0.33-1.26)	3.01 (1.31-6.94)	2.97 (1.29-6.84)	2.86 (1.24-6.61)
	Other/unknown vs white	0.84 (0.68-1.03)	0.83 (0.67-1.03)	0.82 (0.67-1.01)	1.05 (0.49-2.23)	1.04 (0.49-2.21)	1.03 (0.48-2.18)	2.57 (0.92-7.18)	2.55 (0.91-7.14)	2.53 (0.91-7.07)
Charlson Comorbidity Index	1-2 vs 0	1.20 (1.15-1.25)	1.21 (1.16-1.26)	1.24 (1.19-1.30)	1.10 (0.93-1.31)	1.11 (0.94-1.32)	1.15 (0.97-1.37)	1.42 (0.97-2.06)	1.43 (0.98-2.08)	1.47 (1.01-2.14)
	3-4 vs 0	1.36 (1.29-1.44)	1.41 (1.33-1.49)	1.50 (1.42-1.59)	1.43 (1.16-1.76)	1.47 (1.19-1.82)	1.59 (1.28-1.96)	1.30 (0.78-2.17)	1.34 (0.80-2.23)	1.42 (0.85-2.36)
	5+ vs 0	1.53 (1.42-1.64)	1.64 (1.53-1.76)	1.84 (1.72-1.98)	2.31 (1.80-2.96)	2.48 (1.94-3.18)	2.83 (2.21-3.64)	1.24 (0.65-2.37)	1.32 (0.69-2.53)	1.48 (0.77-2.85)
Medicare buy-in	Yes vs no	1.00 (0.93-1.07)	1.01 (0.95-1.09)	1.04 (0.97-1.12)	1.07 (0.86-1.34)	1.09 (0.87-1.36)	1.12 (0.90-1.40)	0.63 (0.37-1.06)	0.63 (0.37-1.08)	0.65 (0.38-1.11)
Cushing syndrome diagnosis	Yes vs no	1.14 (0.53-2.42)	1.16 (0.54-2.49)	1.29 (0.60-2.77)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Hormone replacement therapy	Yes vs no	0.80 (0.59-1.07)	0.80 (0.60-1.08)	0.78 (0.58-1.05)	1.34 (0.50-3.56)	1.35 (0.50-3.60)	1.29 (0.48-3.46)	1.05 (0.15-7.61)	1.06 (0.15-7.67)	1.03 (0.14-7.50)
Osteoporosis diagnosis	Yes vs no	1.74 (1.67-1.81)	1.74 (1.67-1.81)	1.74 (1.67-1.81)	1.43 (1.19-1.71)	1.43 (1.19-1.72)	1.43 (1.19-1.71)	1.79 (1.27-2.51)	1.79 (1.27-2.51)	1.78 (1.27-2.51)
Long-term steroid use	Yes vs no	1.41 (1.06-1.88)	1.44 (1.08-1.92)	1.47 (1.10-1.96)	1.88 (0.72-4.95)	1.90 (0.72-4.99)	1.97 (0.75-5.17)	4.11 (1.05-16.09)	4.18 (1.07-16.38)	4.28 (1.09-16.85)
Injections, n	—	0.96 (0.95-0.96)	0.96 (0.95-0.96)	0.95 (0.94-0.96)	0.95 (0.93-0.98)	0.95 (0.92-0.97)	0.94 (0.91-0.97)	0.91 (0.85-0.97)	0.91 (0.85-0.97)	0.90 (0.85-0.96)

^aRed values, $P < .01$; blue values, $P < .001$.

they may accept ESI as preferable to surgery. In addition, most private payers require extensive nonoperative treatment before they will approve surgery as a treatment option.

In a study by Mandel and colleagues,¹⁴ ESI increased the risk of vertebral compression fractures by 21%, which in turn increased the risk of death.¹⁹ If accurate, these findings obviously would challenge the perception that ESI is a low-risk intervention. In contrast to the Mandel study,¹⁴ the present analysis of the Medicare population revealed no clinically relevant change in risk of osteoporotic spine fracture with each successive ESI after the initial injection. After the initial injection, each successive ESI decreased the relative risk of osteoporotic spine fracture by 2%, and each successive LJSI decreased it by 4%. Although statistically significant, the small change in relative risk may not be clinically relevant. However, taken cumulatively over a number of successive injections, these effects may be clinically relevant.

The data also showed that, after the initial injection, each successive ESI had no effect on risk of osteoporotic hip or wrist fracture, and each successive LJSI reduced the risk. Similar to earlier findings,^{20,21} long-term steroid use increased the risk of spine fracture in ESI and LJSI patients. Prolonged exposure to steroids may be necessary to reduce bone formation and increase bone breakdown.¹²

Although the study by Mandel and colleagues¹⁴ and our study both used administrative databases and survival analysis methods, conclusions differed. First, Mandel and colleagues¹⁴ used a study inclusion criterion of spine-related steroid injections, whereas we used a criterion of any steroid injection. Second, they used 50 years as the lower age for study inclusion, and we used 65 years. Third, to control for patients who had osteoporosis before study entry, they excluded those who had a fracture in an adjacent vertebra after kyphoplasty and vertebroplasty. It is unclear if patients who had osteoporotic fractures at other sites were excluded as well. Thus, the 2 cohorts may not be directly comparable.

Whereas Mandel and colleagues¹⁴ based their definition of osteoporotic spine fracture on a keyword search of a radiology database, we used a specific reportable *ICD-9-CM* diagnosis code. As a result, they may have overreported osteoporotic spine fractures, and we may have underreported. Finally, our sample was much larger than theirs. Given the relative rarity of osteoporotic fractures, a study with a larger sample may have more power to detect differences. In addition, unlike Mandel and

colleagues,¹⁴ we focused on an injection cohort. We did not include or make comparisons with a no-injection cohort because our study hypothesis involved the potential systemic effects of steroid injections based on injection site. Although chronic steroid use was found to have a significant effect in our study, it is unclear to what extent the diagnosis code was used, during the comorbidity assessment or only in the event of steroid-related complications.

Our study also found that, after the initial injection, each successive LJSI decreased the risk of osteoporotic wrist fracture by 10%, and each successive TSI decreased the risk of osteoporotic hip fracture by 5%. It is plausible these injections allowed improved mobility, mitigating the effects of osteoporosis induced by inactivity and lack of resistance training. It is also possible that improved mobility limited falls.

In summary, this analysis of the Medicare claims database revealed that ESI, TSI, and LJSI decreased osteoporotic spine fracture risk. However, the effect was small and may not be clinically meaningful. After the initial injection, successive ESIs had no effect on the risk of osteoporotic hip or wrist fracture, and successive LJSIs reduced the risk of osteoporotic wrist fracture, perhaps because of improved mobility. Prolonged oral steroid use increased spine fracture risk in ESI and LJSI patients. More studies are needed to evaluate the risk-benefit profile of steroid injections.

Dr. Carreon is Clinical Research Director, Norton Leatherman Spine Center, Louisville, Kentucky. Dr. Ong is a Principal Engineer, Biomedical Engineering Practice, Mr. Lau is a Senior Managing Scientist, Epidemiology and Computational Biology Practice, and Dr. Kurtz is a Principal and Practice Director, Biomedical Engineering Practice, Exponent, Inc, Menlo Park, California. Dr. Glassman is an Attending Spine Surgeon, Norton Leatherman Spine Center, Louisville, Kentucky, and a Professor, Department of Orthopaedic Surgery, University of Louisville School of Medicine, Louisville, Kentucky.

Address correspondence to: Leah Y. Carreon, MD, MSc, Norton Leatherman Spine Center, 210 E Gray St, Suite 900, Louisville, KY 40202 (tel, 502-584-7525; fax, 502-589-0849; email, leah.carreon@nortonhealthcare.org).

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