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Association Between Recurrent Fracture Risk and Implementation of Fracture Liaison Services in Four Swedish Hospitals: A Cohort Study

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ABSTRACT

Structured secondary preventions programs, called fracture liaison services (FLSs), increase the rate of evaluation with bone densitometry and use of osteoporosis medication after fracture. However, the evidence regarding the effect on the risk of recurrent fracture is insufficient. The aim of this study was to investigate if implementation of FLS was associated with reduced risk of recurrent fractures. In this retrospective cohort study, electronic health records during 2012 to 2017 were used to identify a total of 21,083 patients from four hospitals in Western Sweden, two with FLS (n = 15,449) and two without (n = 5634). All patients aged 50 years or older (mean age 73.9 [SD 12.4] years, 76% women) with a major osteoporotic index fracture (hip, clinical spine, humerus, radius, and pelvis) were included. The primary outcome was recurrent major osteoporotic fracture. All patients with an index fracture during the FLS period (n = 13,946) were compared with all patients in the period before FLS implementation (n = 7137) in an intention-to-treat analysis. Time periods corresponding to the FLS hospitals were used for the non-FLS hospitals. In the hospitals with FLSs, there were 1247 recurrent fractures during a median follow-up time of 2.2 years (range 0–6 years). In an unadjusted Cox model, the risk of recurrent fracture was 18% lower in the FLS period compared with the control period (hazard ratio = 0.82, 95% confidence interval [CI] 0.73–0.92, p = .001), corresponding to a 3-year number needed to screen of 61, and did not change after adjustment for clinical risk factors. In the hospitals without FLSs, no change in recurrent fracture rate was observed. Treatment decisions were made according to the Swedish treatment guidelines. In conclusion, implementation of FLS was associated with a reduced risk of recurrent fracture, indicating that FLSs should be included routinely at hospitals treating fracture patients. © 2020 The Authors. *Journal of Bone and Mineral Research* published by American Society for Bone and Mineral Research.

KEY WORDS: FRACTURE; FRACTURE LIAISON SERVICE; OSTEOPOROSIS; RECURRENT FRACTURE

Introduction

Fractures, especially hip and vertebral fractures, increase suffering, morbidity, and mortality at high societal and health care costs.[1] At the age of 50 years, the lifetime risk of sustaining a fragility fracture is 50% for women and 20% for men.[2] The risk of recurrent fracture is most pronounced and increased up to five times in the first 2 years after an index fracture.[3,4] Osteoporosis medications such as oral and intravenous bisphosphonates, denosumab, and teriparatide are effective in increasing bone mineral density (BMD) and reduce fracture risk by approximately 40% for hip fractures and by 45% to 70% for vertebral fractures.[5] Despite the proven efficacy of these treatments, the probability to receive osteoporosis medication in the US within a year after hip fracture has declined rapidly from 40.2% in 2002 to 20.5% in 2011.[6]

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To increase osteoporosis medication treatment rates after fracture, structured secondary prevention programs called fracture liaison services (FLSs) have been implemented worldwide.[7] Patients receiving fracture care within an FLS have higher rates of BMD testing, treatment initiation, and better adherence.[8,9] However, the evidence regarding FLS and association with reduced risk of recurrent fracture is insufficient, consisting of smaller studies, studies with short follow-up time, and studies with high risk of various biases.[8–13]

The primary objective of the present study was to investigate if FLS implementation was associated with reduced risk of recurrent fracture, using data from four hospitals in Western Sweden, two with FLSs and two without. Secondary objectives included to investigate the associations between FLS implementation and osteoporosis medication use, fall injuries, and mortality.

Materials and Methods

Study design

This register-based cohort study used hospital electronic patient records in Western Sweden to identify all patients aged 50 years or older with a major osteoporotic fracture (fracture of the wrist, upper arm, hip, vertebra, or pelvis) during 2012 to 2017. All patients with a major osteoporotic fracture during the FLS period were compared with all patients with a major osteoporotic fracture before the FLS implementation. The risk of recurrent fracture was investigated using multivariable Cox models. The FLS hospitals and non-FLS hospitals were analyzed separately, using the same methodology. The study was approved by the regional ethical review board in Gothenburg.

Fracture liaison services

Skaraborg Hospital, a regional hospital serving 265,000 inhabitants, started an FLS on January 1, 2013, and included all patients aged 50 years or older seeking care for a major osteoporotic fracture. All medical secretaries at the emergency and orthopedic departments were instructed to refer patients for a fracture risk assessment, using FRAX,[14] and bone densitometry with dual-energy X-ray absorptiometry (DXA), which were later analyzed by a specialist who sent a treatment recommendation directly to the primary care physician. Starting January 1, 2014, all patients aged 80 years or older with a hip fracture were offered parenteral osteoporosis treatment (zoledronic acid [iv] or denusumab [sc]) in their homes, without prior DXA. A detailed description and evaluation of the first 2 years of this FLS has been described previously.[11]

The Sahlgrenska University Hospital, which serves 715,000 inhabitants in the Gothenburg region, started a similar FLS on July 1, 2014. Patients with major osteoporotic fractures were identified in three ways. First, a coordinator assessed data extracts from the Swedish Fracture Register[15] and excluded malignancies and obvious high-energy fracture events. Second, the radiology department identified and referred vertebral fracture patients to the coordinator. And third, admitted patients with vertebral or hip fractures were offered parenteral osteoporosis treatment without DXA examination before leaving the hospital. The coordinator selected patients for FRAX and DXA examination, which were analyzed by a specialist who sent a treatment recommendation directly to the primary care physician.

At both FLS hospitals, treatment decisions were based on the Swedish treatment guidelines, ie, to consider treatment for patients with (i) previous hip or spine fracture; (ii) other (than hip or spine) previous fracture, a low BMD (*T*-score ≤ −2.0 SD), and FRAX-score ≥ 20% for major osteoporotic fracture; (iii) osteoporosis diagnosis; or (iv) 5 mg of daily oral glucocorticoid treatment for 3 months or more.

Södra Älvsborgs Hospital, a county hospital, serving approximately 201,000 inhabitants within and around the city of Borås, as well as Alingsås Hospital, serving approximately 102,000 inhabitants, did not implement FLSs at any time during the study period. However, in order to study possible temporal trends in the rate of recurrent fracture, we assumed that FLS implementation had occurred for major osteoporotic fractures on the same date as the nearby Sahlgrenska University Hospital (July 1, 2014), thus enabling a comparison of the same time periods as the FLS hospitals.

Ascertainment of fracture

All hospital-based nonmalignant fracture diagnoses in ICD-10 regardless of type of trauma were collected, apart from head fractures. Refinement of the fracture data was performed in several steps. First, if there was a simultaneous code indicating revisit (Z09, Z47, Z48), that fracture diagnosis was discarded. Second, hip fracture diagnoses (cervical S72.0, trochanteric S72.1, or subtrochanteric S72.2) without a simultaneous code for surgical procedure (NFB, NFC, or NFJ) were discarded. Identification of hip fracture in registers using this combination has high accuracy.[16] Third, a washout period of 5 months was used, ie, if a fracture diagnosis on the same skeletal site was repeated within 5 months, the latter diagnosis was excluded. The washout period length has been defined using an X-ray-verified data set in order to maximize accuracy.[11] Finally, in both the pre-FLS and in the FLS period, the first major osteoporosis fracture was designated index fracture and used as baseline. Any subsequent major osteoporotic fracture or hip fracture was considered a recurrent fracture. Recurrent fractures occurring at different hospitals than the hospital of the index fracture were also accounted for. Time to recurrent fracture was censored for moving out of the region, death, or end of study period (December 31, 2017).

Ascertainment of nonskeletal fall injury and death

Using electronic health records from hospitals and primary care, a fall (W00-W19) on the same date as an injury (S00-T14) on an occasion without a fracture (Sx2, T02, T08, T10, T12) was classified as nonskeletal fall injury. Time to such nonskeletal fall injury was also censored for moving out of the region, death, or end of study period (December 31, 2017). Time to death was also censored for moving out of the region or end of study period.

Ascertainment of medical history

Using diagnoses from hospitals and primary care, a 1-year historic window was used to assess both previous medication and previous illnesses, thus including 2011 (Table 1). The regional prescription register was used to identify calcium and vitamin D treatment and osteoporosis medication. To identify nonprescribed parenteral treatment offered to patients at outpatient clinics or while admitted, the combination of an osteoporosis diagnosis (M8) and a code for intravenous (DT016) or subcutaneous (DT021) administration was used. Charlson comorbidity index was calculated to summarize and quantify comorbidity.[17]

Table 1. Characteristics of Patients With Index Major Osteoporotic Fracture During Versus Before the FLS Period, in Hospitals With and Without FLS

	A. Hospitals with FLS			B. Hospitals without FLS		
	Before FLS	During FLS	St. Diff[1]	"Before" FLS	"During" FLS	St. Diff.[1]
	n = 4828	*n* = 10,621	(%)	*n* = 2309	*n* = 3325	(%)
Female sex, *n* (%)	3677 (76.2%)	8128 (76.5%)	0.9	1760 (76.2%)	2521 (75.8%)	0.9
Age (years), mean (SD)	74.2 (12.6)	73.7 (12.4)	3.7	73.7 (12.2)	74.3 (12.1)	4.3
50–67, *n* (%)	1638 (33.9%)	3548 (33.4%)	1.1	786 (34.0%)	1018 (30.6%)	7.3
68–81, *n* (%)	1496 (31.0%)	3638 (34.3%)	7.0	801 (34.7%)	1209 (36.4%)	3.5
82–105, *n* (%)	1694 (35.1%)	3435 (32.3%)	5.8	722 (31.3%)	1098 (33.0%)	3.8
Index fracture site, *n* (%)						
Wrist (S52.5, S52.6)	1934 (40.1%)	4519 (42.5%)	5.1	1034 (44.8%)	1387 (41.7%)	6.2
Shoulder (S42.2)	1171 (24.3%)	2491 (23.5%)	1.9	527 (22.8%)	729 (21.9%)	2.2
Hip (S72.0-S72.2)	395 (8.2%)	697 (6.6%)	6.2	150 (6.5%)	242 (7.3%)	3.1
Vertebra (S22.0, S22.1, S32.0, M48.5)	666 (13.8%)	1530 (14.4%)	1.8	308 (13.3%)	502 (15.1%)	5.0
Pelvis (S32.4, S32.5, S32.7, S32.8)	662 (13.7%)	1384 (13.0%)	2.0	290 (12.6%)	465 (14.0%)	4.2
Any previous fracture (before index), *n* (%)	174 (3.6%)	346 (3.3%)	1.9	88 (3.8%)	114 (3.4%)	2.0
Nonskeletal fall injury (before index), *n* (%)	294 (6.1%)	644 (6.1%)	0.1	137 (5.9%)	212 (6.4%)	1.8
Osteoporosis medication (before index), *n* (%)	427 (8.8%)	872 (8.2%)	2.3	141 (6.1%)	193 (5.8%)	1.3
Of which peroral bisphosphonates, *n* (%)	393 (8.1%)	717 (6.8%)	5.3	139 (6.0%)	173 (5.2%)	3.5
Calcium and vitamin D, *n* (%)	956 (19.8%)	1942 (18.3%)	3.9	364 (15.8%)	512 (15.4%)	1.0
Alcohol-related diseases, *n* (%)	154 (3.2%)	282 (2.7%)	3.2	58 (2.5%)	62 (1.9%)	4.4
Rheumatoid arthritis, *n* (%)	51 (1.1%)	142 (1.3%)	2.6	11 (0.5%)	30 (0.9%)	5.1
Osteoporosis diagnosis, *n* (%)	155 (3.2%)	214 (2.0%)	7.5	40 (1.7%)	49 (1.5%)	2.1
Secondary osteoporosis,[2] *n* (%)	133 (2.8%)	276 (2.6%)	1.0	58 (2.5%)	67 (2.0%)	3.3
Charlson Comorbidity Index, mean (SD)	1.05 (1.54)	1 (1.56)	3.6	0.97 (1.47)	1.08 (1.69)	7.0
=0, n (%)	2490 (51.6%)	5765 (54.3%)	5.4	1252 (54.2%)	1764 (53.1%)	2.3
=1, n (%)	1016 (21.0%)	2129 (20.0%)	2.5	443 (19.2%)	640 (19.2%)	0.2
≥2, n (%)	1322 (27.4%)	2727 (25.7%)	3.9	614 (26.6%)	921 (27.7%)	2.5
Charlson comorbidity index components:						
Dementia, n (%)	411 (8.5%)	786 (7.4%)	4.1	164 (7.1%)	242 (7.3%)	0.7
Ischeamic heart disease, n (%)	647 (13.4%)	1131 (10.6%)	8.5	255 (11%)	372 (11.2%)	0.5
Heart failure, n (%)	451 (9.3%)	899 (8.5%)	3.1	203 (8.8%)	289 (8.7%)	0.4
Cerebrovascular disease, n (%)	474 (9.8%)	870 (8.2%)	5.7	207 (9.0%)	311 (9.4%)	1.3
Vascular diseases, n (%)	163 (3.4%)	314 (3.0%)	2.4	62 (2.7%)	97 (2.9%)	1.4
Chronic pulmonary diseases, n (%)	566 (11.7%)	1065 (10.0%)	5.4	248 (10.7%)	346 (10.4%)	1.1
Chronic liver disease, n (%)	48 (1.0%)	118 (1.1%)	1.1	23 (1.0%)	19 (0.6%)	4.8
Tumor without metastasis, n (%)	422 (8.7%)	878 (8.3%)	1.7	216 (9.4%)	324 (9.7%)	1.3
Lymphoma or leukemia, n (%)	46 (1.0%)	119 (1.1%)	1.7	12 (0.5%)	26 (0.8%)	3.3
Diabetes, n (%)	596 (12.3%)	1350 (12.7%)	1.1	289 (12.5%)	429 (12.9%)	1.2
With end organ damage, n (%)	140 (2.9%)	400 (3.8%)	4.8	47 (2.0%)	136 (4.1%)	11.9
Kidney disease, n (%)	154 (3.2%)	368 (3.5%)	1.5	68 (2.9%)	180 (5.4%)	12.4
Moderate or severe, n (%)	33 (0.7%)	119 (1.1%)	4.6	13 (0.6%)	54 (1.6%)	10.2
Hemiplegia, n (%)	22 (0.5%)	77 (0.7%)	3.5	6 (0.3%)	12 (0.4%)	1.8
Peptic ulcer disease, n (%)	52 (1.1%)	100 (0.9%)	1.4	21 (0.9%)	32 (1.0%)	0.5
Metastatic solid tumor, n (%)	52 (1.1%)	136 (1.3%)	1.9	25 (1.1%)	55 (1.7%)	4.9

Patient characteristics at baseline, ie, the time of index fracture, the starting point of the FLS. All medical history data have a 1-year historic window from baseline. ATC and ICD codes as well as Charlson comorbidity weights are specified in Supplemental Table SS1.

[1] St. Diff. = standardized difference = $|\text{mean}_1\text{-mean}_2|/\sqrt{(\sigma_1^2 + \sigma_2^2)/2)}$, St. Diff. < 10% indicate relatively small imbalances.

[2] Secondary osteoporosis includes insulin-dependent diabetes mellitus, hyperparathyroidism, hyperthyroidism, hypogonadism, malnutrition, osteogenesis imperfecta, or chronic liver disease.

Statistical analyses

To assess differences in baseline characteristics, standardized differences were calculated.[18] For a given covariate, a standardized difference of less than 10% indicates a relatively small imbalance.[18] Confidence intervals for event rates were calculated assuming Poisson distributions. To investigate the association between participation in FLS and recurrent fracture risk, a Cox proportional hazards model starting at baseline was used. In contrast to logistic regression, the Cox regression model uses the length of each individual's follow-up period. Cox analyses were performed for major osteoporotic fracture, hip fracture, nonskeletal fall injury, and death. The multivariable Cox model was adjusted for age, sex, type of index fracture, any

Table 2. Risk of Recurrent Fracture After Major Osteoporotic Index Fracture

	A. Hospitals with FLS			B. Hospitals without FLS		
	Before FLS	During FLS	*p* Value	"Before" FLS	"During" FLS	*p* Value
No. of patients with index fractures, *n*	*n* = 4828	*n* = 10,621		*n* = 2309	*n* = 3325	
Time at risk, median (range min-max), years	4.32 (0–6)	1.70 (0–5)		4.36 (0–6)	1.48 (0–3.50)	
Major osteoporotic fracture						
No. (%)	621 (12.9)	626 (5.9)		299 (12.9)	214 (6.4)	
Per 1000 person-years (95% CI)	35.8 (33.0–38.7)	33.7 (31.1–36.5)		35.1 (31.3–39.4)	43.6 (37.9–49.8)	
Unadjusted HR (95% CI)	1 (Reference)	0.82 (0.73–0.92)	.001	1 (Reference)	1.10 (0.91–1.33)	.34
HR adjusted for age and sex (95% CI)	1 (Reference)	0.82 (0.73–0.92)	.001	1 (Reference)	1.08 (0.89–1.30)	.45
Multivariable[1] adjusted HR (95% CI)	1 (Reference)	0.83 (0.73–0.93)	.001	1 (Reference)	1.08 (0.89–1.30)	.46
3-year multivariable[1] adjusted ARR	Reference	1.7	.001			
5-year multivariable[1] adjusted ARR	Reference	2.5	.001			
3-year multivariable[1] adjusted NNS	Reference	61	.001			
5-year multivariable[1] adjusted NNS	Reference	40	.001			
Hip fracture						
No. (%)	66 (1.4)	74 (0.7)		28 (1.2)	22 (0.7)	
Per 1000 person-years (95% CI)	3.6 (2.7–4.5)	3.8 (3.0–4.8)		3.1 (2.0–4.5)	4.3 (2.7–6.5)	
Unadjusted HR (95% CI)	1 (Reference)	0.79 (0.56–1.12)	.18	1 (Reference)	1.07 (0.58–1.94)	.84
HR adjusted for age and sex (95% CI)	1 (Reference)	0.80 (0.56–1.13)	.20	1 (Reference)	1.02 (0.56–1.87)	.94
Multivariable[a] adjusted HR (95% CI)	1 (Reference)	0.82 (0.58–1.15)	.25	1 (Reference)	0.98 (0.54–1.79)	.94

[1] Multivariable = age, sex, type of index fracture, previous fracture, previous fall injury, osteoporosis diagnosis, secondary osteoporosis, rheumatoid arthritis, osteoporosis medication, calcium/vitamin D, alcohol-related diseases, and Charlson comorbidity index.

previous fracture, previous nonskeletal fall injury, osteoporosis diagnosis, secondary osteoporosis, rheumatoid arthritis, osteoporosis medication, calcium and vitamin D, alcohol-related diseases, and Charlson comorbidity index. For the main outcome, major osteoporotic fracture, interactions between FLS participation and sex, tertile of age, and Charlson (ordinal) were tested, respectively. Subgroup analyses were also performed per sex, tertile of age, and Charlson stratum (0, 1, ≥2), as well as separated by hospital. The Cox assumption of proportional hazards was tested using a time-dependent Cox model with a linear interaction term between time and FLS group. To investigate if the difference in follow-up time between the groups affected the result, a sensitivity analysis was performed censoring the Cox model at 2 years. Competing risk regression analysis was performed using the subdistribution hazard function developed by Fine and Gray.[19] Incident rates of recurrent fracture were calculated per year of recurrence for the non-FLS hospitals to show secular trend. A Cox model stratified by hospital (all four hospitals) and including date of index fracture and FLS-indicator (1/0), was used to determine if there was a secular trend, which could influence the association between FLS and recurrent fracture. For treatment-naïve patients, adherence to osteoporosis medication was calculated per year since initiation as total time with treatment divided by total follow-up time. Statistical analyses were performed using IBM (Armonk, NY, USA) SPSS software, version 22, and Stata version SE 16.0 for Mac (StataCorp, College Station, TX, USA). Significance testing was two-sided and a *p* value less than 0.05 was considered significant.

Analyses to address potential bias

Potential selection bias was addressed in three ways. First, known risk factors for fracture and morbidity were examined at the time for index fracture and no clinically relevant differences between groups should be expected. Second, the Cox hazard

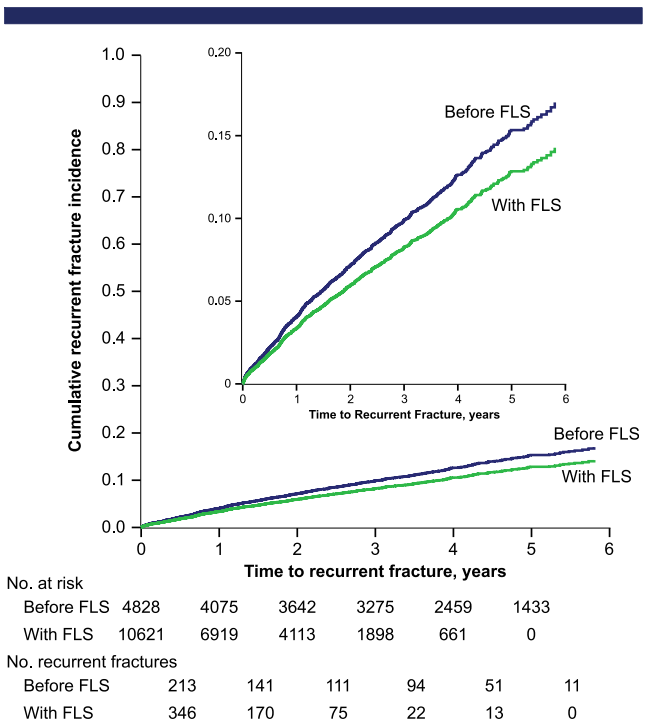

Fig. 1. Cumulative hazard of recurrent fracture with FLS compared with the period before the FLS at the two FLS hospitals. The Cox regression model was adjusted for age, sex, type of index fracture (wrist, humerus, hip, vertebral, pelvic), any previous fracture, previous nonskeletal fall injury, osteoporosis diagnosis, secondary osteoporosis, rheumatoid arthritis, osteoporosis medication, calcium and vitamin D supplementation, alcohol-related diseases, and Charlson comorbidity index. Medical history is derived using a 1-year window in the registers. Recurrent fracture includes wrist, humerus, hip, vertebral, and pelvic fractures. The inset shows the same data on an enlarged *y*-axis.

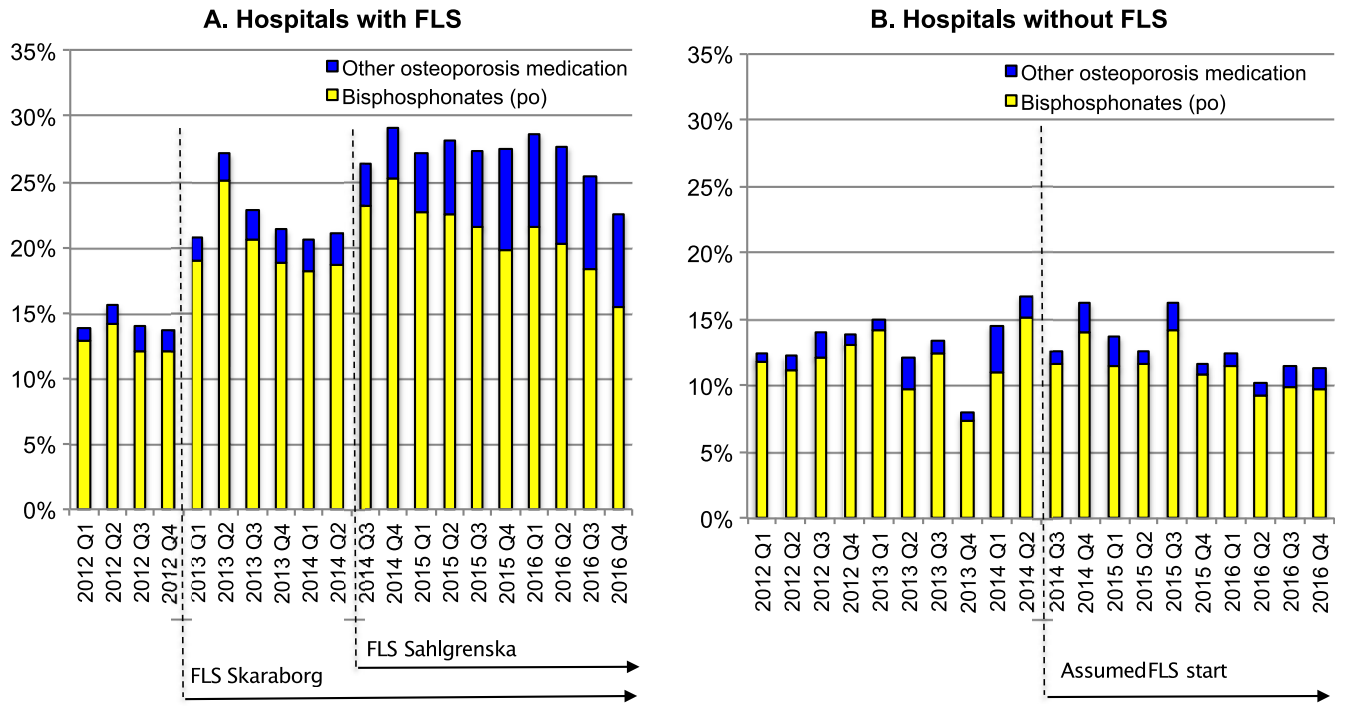

Fig. 2. Proportion (%) of patients receiving treatment with osteoporosis medication within 1 year of index fracture at hospitals with FLSs (*A*) and without FLSs (*B*).

models were adjusted for known risk factors for fracture and Charlson comorbidity index, where the adjustment was not expected to change the association. Third, the risk to suffer a nonskeletal fall injury was investigated, and equal risks of falls would be expected, if frailty was similar in the compared groups. Finally, to account for possible temporal bias, ie, changes in recurrent fracture rate due to time passing, two nearby hospitals in which no FLS implementation had occurred were analyzed, using both the multivariable Cox model and incident rates of recurrent fracture per year. Also, in a sensitivity analysis, the follow-up time was censored at 2 years to assess whether the difference in follow-up time between the two groups affected the result.

Role of the funding sources

This study was funded by the Swedish Research Council (VR) and ALF/LUA grants from the Sahlgrenska University Hospital. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

Results

The present study included 21,083 patients with index fracture, with a total follow-up time of 52,429 patient years. The FLS hospitals included 4828 patients followed a total of 18,701 years before FLS implementation and 10,621 patients who were included in the FLS period and followed a total of 19,411 years. The two reference hospitals without FLSs included 2309 patients before the assumed FLS implementation and were followed a total of 9138 years, whereas 3325 patients with an assumed FLS were followed a total of 5143 years. Thus, because of the study design, patients before the FLS were fewer and had longer follow-up time than the patients included during the FLS periods.

Baseline characteristics (at the time of index fracture) were similar between patients included before and during the FLSs in both the FLS hospitals (Table 1*A*) and the non-FLS hospitals (Table 1*B*). All standardized differences were less than 10% (Table 1). A comparison of the FLS hospitals and the reference hospitals, pre-/post-FLS periods combined, showed similar baseline characteristics. The use of osteoporosis medication at baseline was slightly higher in the FLS hospitals (8.4% versus 5.9%). This was also true for calcium and vitamin D supplementation (18.8% versus 15.5%), but all standardized differences between the hospitals were lower than 10% (Supplemental Table S2).

FLS implementation was associated with reduced risk of recurrent fracture

In the FLS hospitals, using a Cox proportional hazards model, the risk of recurrent major osteoporotic fracture was 18% lower in the FLS period compared with the period before implementation (HR = 0.82, 95% CI 0.73–0.93, $p < .001$). The result was not affected by multivariable adjustment (Table 2*A*; Fig. 1), nor by early censoring after 2 years of follow-up (HR = 0.83, 95% CI 0.73–0.95, $p = .008$). When applying Fine and Gray's competing risk of death regression to the multivariate model, the association remained, with a subdistribution hazard ratio of 0.73 (95% CI 0.66–0.82, $p < .001$). Using the multivariable-adjusted Cox model, the 3-year and 5-year number needed to screen (NNS)

Table 3. Chance of Osteoporosis Medication and Risk of Nonskeletal Fall Injury and Death after Major Osteoporotic Index Fracture

	A. Hospitals with FLS			B. Hospitals without FLS		
	Before FLS	During FLS	*p* Value	"Before" FLS	"During" FLS	*p* value
No. of patients with index fractures, *n*	*n* = 4828	*n* = 10,621		*n* = 2309	*n* = 3325	
Time at risk, median (range min-max), years	4.32 (0–6)	1.70 (0–5)		4.36 (0–6)	1.48 (0–3.5)	
Osteoporosis medication treatment initiation						
No. (%)	1107 (22.9)	2820 (26.6)		380 (16.5)	414 (12.5)	
Per 1000 person-years (95% CI)	72.8 (68.5–77.2)	199.6 (192.3–207.1)		48.7 (43.9–53.9)	91.3 (82.7–100.5)	
Unadjusted HR (95% CI)	1 (Reference)	1.65 (1.54–1.78)	<.001	1 (Reference)	0.99 (0.86–1.14)	.85
HR adjusted for age and sex (95% CI)	1 (Reference)	1.67 (1.55–1.80)	<.001	1 (Reference)	0.98 (0.85–1.13)	.78
Multivariable[1] adjusted HR (95% CI)	1 (Reference)	1.62 (1.51–1.75)	<.001	1 (Reference)	1.02 (0.89–1.18)	.74
Nonskeletal fall injury						
No. (%)	801 (16.6)	1019 (9.6)		379 (16.4)	288 (8.7)	
Per 1000 person-years (95% CI)	47.4 (44.1–50.8)	56.6 (53.2–60.2)		45.8 (41.3–50.7)	59.8 (53.1–67.2)	
Unadjusted HR (95% CI)	1 (Reference)	1.02 (0.93–1.13)	.68	1 (Reference)	1.08 (0.91–1.27)	.39
HR adjusted for age and sex (95% CI)	1 (Reference)	1.02 (0.93–1.13)	.64	1 (Reference)	1.06 (0.90–1.25)	.51
HR adjusted for age, sex, previous fall injury and Charlson comorbidity index (95% CI)	1 (Reference)	1.02 (0.93–1.13)	.69	1 (Reference)	1.06 (0.90–1.25)	.49
Death						
No. (%)	1701 (35.2)	1832 (17.2)		701 (30.4)	527 (15.8)	
Per 1000 person-years (95% CI)	91 (86.7–95.4)	94.4 (90.1–98.8)		76.7 (71.1–82.6)	102.5 (93.9–111.6)	
Unadjusted HR (95% CI)	1 (Reference)	0.94 (0.88–1.01)	.11	1 (Reference)	1.21 (1.06–1.37)	.003
HR adjusted for age and sex (95% CI)	1 (Reference)	0.96 (0.89–1.03)	.23	1 (Reference)	1.14 (1.00–1.29)	.04
HR adjusted for age, sex and Charlson comorbidity index (95% CI)	1 (Reference)	0.96 (0.90–1.03)	.30	1 (Reference)	1.09 (0.97–1.24)	.16

[1] Multivariable = age, sex, type of index fracture, previous fracture, previous fall injury, osteoporosis diagnosis, secondary osteoporosis, rheumatoid arthritis, osteoporosis medication, calcium/vitamin D, alcohol-related diseases and Charlson comorbidity index.

were 61 and 40, respectively (Table 2*A*). A conservative post hoc statistical power calculation using the smallest group size ($n = 4828$), the incidence of the FLS group (5.9%), the HR of the Cox model (0.82), and an alpha value of 0.05 yields a power of 95%. While not significant, the risk of hip fracture was also lower (Table 2*A*) in the FLS period than in the period before. In the non-FLS hospitals, no significant associations were found between the period before and during the assumed FLS for recurrent fracture (Table 2*B*). There was no apparent secular trend in recurrent fracture incident rate in the two non-FLS hospitals (Supplemental Fig. SS1). In a multivariable-adjusted Cox regression using data from all four hospitals, with stratification by hospital and added adjustment for index date, the association between FLS implementation and risk of recurrent fracture was maintained (HR = 0.82, 95% CI 0.70–0.97, $p = .02$) and index date was not significantly associated with recurrent fracture ($p = .96$).

Treatment rates after index fracture

In the FLS hospitals, osteoporosis medication treatment rates within 1 year after index fracture increased significantly from 14.7% to 28.0% ($p < .001$) after FLS implementation, and the proportion of parenteral treatment increased from 11.8% to 18.9%. In the hospitals without FLSs, there were no significant changes in treatment rates before (13.3%) versus after (12.9%), $p = .73$, the assumed FLS implementation. Osteoporosis medication treatment rates after fracture did not differ between the FLS (14.7% versus 13.3%, $p = .10$) and non-FLS hospitals before FLS implementation, whereas after FLS implementation a larger proportion of fracture patients were treated at the FLS hospitals than at the non-FLS hospitals (28.0% versus 12.9%, $p < .001$) (Fig. 2). In a Cox proportional hazards model with osteoporosis medication as endpoint, the chance of receiving osteoporosis medication in the FLS hospitals was 65% higher in the FLS period than in the period before the FLS (HR = 1.65, 95% CI 1.54–1.78, $p < .001$), a result that was not affected by multivariable adjustment (Table 3*A*). In the non-FLS hospitals, no significant association was found (Table 3*B*). Both FLS and non-FLS hospitals demonstrated similar patterns of adherence (Supplemental Fig. S2).

Nonskeletal fall injury and mortality

In the FLS hospitals, both unadjusted and adjusted Cox models revealed that there was no association between incident nonskeletal fall injury and FLS implementation (unadjusted HR = 1.02, 95% CI 0.93–1.13, $p = .68$; Table 3*A*). FLS implementation was not significantly associated with mortality (HR = 0.94, 95% CI 0.88–1.01, $p = .11$; Table 3*A*). In the non-FLS hospitals, assumed FLS implementation was not significantly associated with nonskeletal fall-injury or death (Table 3*B*).

Association between FLS implementation and recurrent fracture per hospital

The associations between recurrent risk of major osteoporotic fracture and FLS remained when analyzed per FLS hospital: Skaraborg

HR = 0.75, 95% CI 0.61–0.93, $p = .008$, and Sahlgrenska HR = 0.84, 95% CI 0.73–0.98, $p = .03$, respectively (Supplemental Table S3).

Interactions and stratification by age, Charlson comorbidity index, and sex

In the FLS hospitals, using a multivariable-adjusted Cox analysis, there were no significant interactions between FLS implementation and sex ($p = .23$), Charlson comorbidity index ($p = .12$), and age ($p = .15$), respectively. For the highest tertile of age (82 to 105 years), FLS implementation was associated with a 26% significant risk reduction of recurrent fracture with a number needed to screen of 23 (3 years) and 16 (5 years). Subgroup analysis per tertile of Charlson comorbidity index, age, and sex are presented in Supplemental Tables S4–S6.

Discussion

In the present study, we found that patients with a major osteoporotic fracture at two Swedish hospitals during an FLS period had 18% reduced risk of recurrent fracture compared with patients in the period before the FLS implementation. The risk of recurrent fracture did not change during the same time period at two non-FLS hospitals examined. Treatment rates with osteoporosis medication increased by 65% and FLS implementation was not associated with an increased risk of nonskeletal fall injury, indicating that the reduced risk of recurrent fracture may be due to an effect of increased use of osteoporosis medication.

Because age is an important factor for absolute risk of fracture, we sought to investigate whether age had an impact on the association between FLS implementation and risk of recurrent fracture. In subgroup analysis, the association only remained significant among the oldest tertile (aged 82 to 105 years). However, no significant interaction between FLS and age was observed and the study was not adequately powered for subgroup analysis. In particular, few cases of recurrent fractures were observed among the younger patients due to the low absolute risk and the short follow-up time. We therefore caution against drawing conclusions regarding lack of efficacy among the younger patients.

Comparing our study to other studies on recurrent fracture after FLS implementation, the 18% reduced risk reported herein is very similar to the 20% reduction reported by Sietsema in a study of 1312 FLS patients compared with 1312 well-matched controls. However, a post hoc power analysis suggests that the study was underpowered.[12] Dell and colleagues implemented a comprehensive program to screen for osteoporosis, also including other risk groups than prior fracture, and reported a 37% average reduction in actual hip fracture rate compared with pre-program historic controls.[20] Huntjens and colleagues found a 56% reduced risk of recurrent fracture after following 1412 patients for 2 years, only using a different hospital as control, without reporting baseline characteristics such as risk factors, previous osteoporosis medication, and comorbidities.[10] Goltz studied the risk of recurrent fracture in an FLS for 2455 patients with manifest osteoporosis and compared with matched controls not enrolled in the FLS program.[13] No association with recurrent risk was found; however, only scarce information on baseline characteristics were provided.[13] Axelsson and colleagues had insufficient follow-up time to investigate risk of recurrent fracture.[11] Other studies were substantially underpowered.[9] In contrast to previous studies, we used historic controls from the same hospital and controlled thoroughly for baseline characteristics in the analyses. However, a study design using historic controls could be limited and biased if there are temporal trends present. Therefore, we performed analysis to check for any temporal trends. This analysis did not provide any evidence for temporal trends in the rate of recurrent fracture, indicating that the lower recurrent fracture risk observed in the FLS period is due to the FLS implementation itself.

In an effort to assess if the obtained results regarding the magnitude of association between FLS implementation and risk of recurrent fracture presented herein are reasonable, the effect observed in randomized placebo-controlled trials of the osteoporosis medications taken in this study should be considered. In patients with prior fracture, alendronate treatment reduces the risk of spine and hip fracture by 45% and 53%, respectively.[21] Since only a proportion of patients in the FLS period will be eligible and receive osteoporosis medication, the herein observed 18% reduction in recurrent fracture appears reasonably probable.

The study has limitations. First, the observational design prevents assessment of causality. Second, the fracture definitions were based on register data, without guarantees that all fractures were X-ray verified. However, available electronic health records enabled us to conduct a large study with the same methodology, including fracture definitions, for both the FLS and non-FLS hospitals and for the FLS and non-FLS periods. Third, the patients before the FLS were fewer and had longer follow-up time than the patients during the FLS period. However, the Cox model is able to account for such an imbalance, and when censoring the Cox model at 2 years' follow-up, the associations remained. Fourth, although the registers are reliable regarding prescribed per-oral treatments, parenteral treatment is likely underestimated. In Western Sweden, during 2012 to 2017, the total yearly use of 5 mg of zoledronic acid increased from 1063 to 3958 units and of 60 mg of denosumab from 677 to 2092 units. Thus, not all units were registered in a way enabling us to identify the individual patients, only 47% and 36%, respectively. However, this does not affect the result regarding risk of recurrent fracture. Fifth, we did not have access to reliable information on trauma type; however, evidence shows that trauma type does not discriminate osteoporotic from non-osteoporotic fractures.[22] Sixth, the results are dependent on fracture risk and guidelines in Sweden and may not be generalizable to other geographic settings.

Strengths of this study include the mere size of the study and that the same methodology for data collection and analysis was used for all hospitals and time periods. It is, to our knowledge, the largest yet. Because an intention-to-treat analysis approach was used, all men and women with an index fracture were included, which minimizes the risk of selection bias. In support of this argument, we found no substantial differences in baseline characteristics between the FLS patients and the historic controls, and the associations did not change after adjustment for multiple covariates and comorbidity. Patient medical history included data from primary care, which allows for a well-documented baseline with comorbidity data and most FRAX risk factors.[14] The lack of association between FLS and incident nonskeletal fall injury suggests that the FLS association with risk of recurrent fracture is due to increased use of osteoporosis medication, rather than differences in general frailty causing falls. Also, analysis accounting for the competing risk of mortality confirmed the association between FLS and recurrent fracture. Finally, the lack of associations in a nearby hospital with similar

baseline characteristics, but without FLS, indicates lack of temporal trends in recurrent fracture.

In conclusion, FLS implementation was associated with an 18% reduction of recurrent fracture, independently of confounders, indicating that FLSs should be implemented as a part of standard fracture hospital care.

Disclosures

KFA has received lecture fees from Lilly, Meda/Mylan, and Amgen. ML has received lecture fees from Amgen, Lilly, UCB Pharma, Radius Health, Meda, GE-Lunar, and Santax Medico/Hologic. KFA and ML are champions of two of the described FLSs (Skaraborg and Sahlgrenska University Hospital, respectively) in the study. All other authors state that they have no conflicts of interest.

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Authors' roles: KFA, HJ, and ML designed the study. KFA, DL, MM, and ML collected the data. KFA and ML analyzed and interpreted the data. KFA and ML drafted the manuscript. Content revisions were provided by DL, MM, and HJ. All authors approved the final version. KFA and ML take responsibility for the integrity of the data analysis.

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