



Risk of imminent fracture following a previous fracture in a Swedish database study

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Abstract

Summary This study examined the imminent risk of a future fracture within 1 and 2 years following a first fracture in women aged 50 years and older and assessed independent factors associated with risk of subsequent fractures. The study highlights the need to intervene rapidly after a fracture to prevent further fractures.

Introduction This study aims to determine the imminent risk of subsequent fractures within 1 and 2 years following a first fracture and to assess independent factors associated with subsequent fractures.

Methods Retrospective, observational cohort study of women aged ≥ 50 years with a fragility fracture was identified from Swedish national registers. Clinical/demographic characteristics at the time of index fracture and cumulative fracture incidences up to 12 and 24 months following index fracture were calculated. Risk factors for subsequent fracture were identified using multivariate regression analysis.

Results Two hundred forty-two thousand one hundred eight women (mean [SD] age 74 [12.5] years) were included. The cumulative subsequent fracture incidence at 12 months was 7.1% (95% confidence interval [CI], 6.9–7.2) and at 24 months was 12.0% (95% CI, 11.8–12.1). The rate of subsequent fractures was highest in the first month (~15 fractures per 1000 patient-years) and remained steady between 4 and 24 months (~5 fractures/1000 patient-years). Higher age was an independent risk factor for imminent subsequent fractures (at 24 months, sub-distribution hazard ratio [HR], 3.07; $p < 0.001$ for women 80–89 years [reference 50–59 years]). Index vertebral fracture was a strong independent risk factor for subsequent fracture (sub-distribution HR, 2.72 versus hip fracture; $p < 0.001$ over 12 months; HR, 2.23; $p < 0.001$ over 24 months).

Conclusions Our findings highlight the need to intervene rapidly after any fragility fracture in postmenopausal women. The occurrence of a fragility fracture provides healthcare systems with a unique opportunity to intervene to reduce the increased risk of subsequent fractures.

Keywords Fracture risk · Fragility fracture · Near-term · Osteoporosis

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Introduction

Fragility fractures due to osteoporosis are common. More than nine million fragility fractures have been estimated worldwide based on the year 2000 [1], and in Europe, 3.5 million fragility fractures were reported to occur annually [2]. In a study of patient records in Malmö, Sweden, for women aged 50 years, the lifetime probability of a fragility fracture was 23% for hip fracture and 15% for clinical vertebral fracture [3]. Moreover, the number of fragility fractures is expected to rise as the population ages, and in Europe, a 28% increase in the number of fragility fractures has been estimated by 2025 [4].

Fragility fractures cause substantial individual burden related to the significant reduction in a patient's mobility, function, and quality of life [5, 6]. The increase in morbidities associated with fragility fractures is greater than can be attributed to aging alone and represents a major clinical problem [7]. Fragility fractures also lead to an increase in mortality [8–12]. Consequently, an understanding of the variables leading to fracture is an important area of research, to enable treatment strategies to focus on those most at risk and effectively reduce the clinical burden of disease.

Multiple factors are known to increase the risk of sustaining a fragility fracture [13]. Among them, prior fragility fracture is a well-documented major risk factor for future fragility fracture [13–17]. On average, the risk of future fracture is doubled in the presence of a prior fracture [18–20]. In the Reykjavik study of 30,795 men and women, the risk of a second major osteoporotic fracture (MOF) within the year following the first fracture was 2.7-fold higher than the risk seen in the whole of the study population [21]. In addition, a significant number of patients who sustain a hip or wrist fracture have a history of up to three previous fractures [22].

The risk of a subsequent fracture changes over time, and the time elapsed since sustaining a prior fracture is now recognized as an important factor influencing subsequent fracture risk. The concept of “imminent risk” for fracture, defined as a markedly elevated risk of fracture within the next 12–24 months, has been emphasized [19, 23, 24]. In a study of postmenopausal women in The Netherlands, the risk of subsequent fracture was highest within the first year following the initial fracture [25]. This risk decreased over time, but remained higher compared with the whole of the study population during the follow-up period. Age is also an independent predictor of future fracture [21, 26]. In a study of women in the USA, the incidence of any clinical fracture at 1 and 2 years following the initial fracture was 10% and 18%, respectively [26], but the corresponding figures for women ≥ 75 years of age were higher, with a 2-year fracture risk of 25%. All-cause mortality is also highest in the year following a hip fracture [5, 10, 23, 27, 28].

Tools to assess the risk of fragility fracture are extensively used to make clinical decisions [29–31]. FRAX[®], University

of Sheffield, in particular allows the identification of patients at high risk for fracture more effectively than bone mineral density (BMD) measures alone [32]. Accordingly, FRAX has proved useful in identifying individuals at risk of fracture over 10 years and assisting therapeutic decisions, but at present does not take into account the time since fracture or fracture location and was not primarily designed to identify patients at imminent risk of fracture. However, a recent publication suggests that FRAX could be adapted to predict fracture over a shorter period [33]. The need for research to identify the determinants of imminent fracture risk was recently reported in a consensus meeting for the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [24].

Currently, many patients do not receive treatment for their osteoporosis after a fragility fracture, despite the recognition that sustaining a fracture increases the risk of a subsequent fracture [2, 13, 21, 34, 35]. Therefore, a more robust approach to the identification of patients at imminent risk of fracture is important and could prove relevant to determine the best treatment strategies for patients at increased fracture risk. This approach should also include other independent factors that may increase the risk of imminent fracture and may provide insights into a select group of patients in whom rapid intervention to decrease fracture risk is essential.

The aim of the current study was to determine the incidence of subsequent fractures within 1 and 2 years following a first fracture in a population-based study of women in Sweden, and to assess independent factors associated with subsequent fracture. This large-scale Swedish study was designed to strengthen the knowledge around the driving factors for imminent fracture risk.

Methods

Study participants

This was a retrospective, observational cohort study of women with a fragility fracture. Study participants were women aged ≥ 50 years with a fragility fracture at any skeletal location, between the dates 1 July 2006 and 31 December 2012. Women were identified from the National Patient Register (Patientregistret; NPR). The NPR contains patient, geographic, administrative, and medical data for all inpatient and outpatient hospital care in Sweden.

The NPR and the Swedish Prescribed Drug Register (Läkemedelsregistret; PDR) were used to collect data on demographic and potential clinical risk factors for fracture. The PDR contains information on all prescriptions filled at pharmacies in Sweden and is updated monthly; it also contains information on gender, age, and residency of the patients. Date of patient death was obtained from the Cause of Death

Register. The register includes statistics on causes of deaths for all of Sweden. All three registers are held by the Swedish Board of Health and Welfare. Complete data from all of the registers up until 31 December 2012 were available for analysis for all patients included in the study population.

To exclude other potential pathologic causes of fracture, women with a diagnosis of Paget's disease, or a malignancy (other than basal cell carcinoma) at any time during the study, were excluded from the analysis.

Study design

In this retrospective, observational cohort study, clinical and demographic characteristics were collected at the time of the first (index) fracture for each woman included in the analysis. As fractures could not be definitively confirmed to be fragility fractures as opposed to non-fragility fractures using the NPR, only fractures typically associated with osteoporosis were included; the fracture types and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes are shown in Supplementary Table S1. Only clinically diagnosed and coded fractures were included in the analysis; therefore, it is likely that asymptomatic radiographic vertebral fractures were not captured. A main diagnosis of fracture was required for inclusion in the analysis and for the identification of new fractures. The following inclusion criteria were used to differentiate new fracture occurrences from existing fractures recorded at follow-up visits and/or from patient history: (a) when a fracture was registered in the outpatient and inpatient setting on the same day, only the inpatient record was counted; (b) for hip fractures, an inpatient hospital admission was required; (c) fractures at the same location in the body were required to have occurred at least 6 months apart and accompanied by a hospitalization; (d) fractures coded as M80 (osteoporosis with pathologic fracture) were counted only if they were a patient's first fracture. As such, the M80 code for fracture was only used for the index fracture and not for identification of subsequent fractures. Fractures with a code of Z.094 (follow-up examination after fracture) were excluded.

The primary study endpoint was the cumulative incidence of subsequent fracture over 12 months following index fracture. Incidence of subsequent fracture over 24 months was also investigated. The risk of subsequent fracture from the time of the index fracture was estimated by index fracture type, i.e., any fracture, vertebral, hip, non-hip/non-vertebral (NH/NV), and MOF (i.e., vertebral, hip, humerus, or wrist). Independent risk factors for fracture were evaluated.

Data analysis

Cumulative fracture incidences at up to 12 months and 24 months were calculated taking the competing risk of death

into account. The cumulative incidence function is preferred over a Kaplan-Meier estimate when competing events are present, as Kaplan-Meier estimates consider failures due to the competing event as censored, despite the competing event precluding failure from the event of interest altogether [36, 37]. A Kaplan-Meier estimate would therefore overestimate the true risk of fracture in the presence of competing risks.

Clinical and demographic factors associated with subsequent fracture risk were identified using multivariate competing risk regression, with fracture as the outcome and death as the competing event [38]. The variables included in the final multivariate model were age, index fracture type, and Charlson comorbidities. Osteoporosis treatment, glucocorticoid use, drugs associated with the risk of falls, and assisted drug dispensing (based on any filled prescription within 12 months before the index date) were also included in the multivariate model. The full list of variables considered for inclusion in the multivariate model is shown in Supplementary Table S2. Osteoporosis treatments included in the multivariate analysis were bisphosphonates, denosumab, strontium ranelate, raloxifene, and teriparatide (full list shown in Supplementary Table S3). Drugs delivered intravenously or subcutaneously may not have been included if they were dispensed through the hospital clinic and not by prescription. Drugs associated with increased risk of falls were defined using the listed medications from the Swedish National Board of Health and Welfare (Supplementary Table S4) [39]. Glucocorticoid use was defined in the same way as in the FRAX algorithm, i.e., current exposure to oral glucocorticoids or previous exposure to oral glucocorticoids for > 3 months at a dose of prednisolone 5 mg daily or more (or equivalent doses of other glucocorticoids). Assisted drug dispensing was defined as use of the ApoDos system [40]. This is a system where medication is pre-packaged in small bags for morning, lunch, dinner, and evening. Use of the ApoDos system was implemented as a broad proxy for dependency, frailty, medication burden, and cognitive impairment.

Univariate analyses were performed for each of the potential risk factors individually to assess the influence of the risk factor on the risk of subsequent fracture. Sub-distribution hazard ratios (HR) with p values < 0.05 were considered statistically significant and were included in the multivariate model.

No imputation was required for missing data, as data were available for all risk factors used in the models.

Results

Patient characteristics at index date

Patient characteristics at the time of the index fracture are shown in Table 1. After excluding 31,896 women

with either a diagnosis of Paget's disease or a malignancy (other than basal cell carcinoma), a total of 242,108 women (mean [SD] age 74 [12.5] years) with an index fragility fracture were included in the analysis. The number and proportion of fracture types at index date were hip (51,904 [21.4%]), vertebral (15,065 [6.2%]), NH/NV (175,139 [72.3%]), and MOF (vertebral, hip, pelvis, humerus, forearm, or wrist; 156,253 [64.5%]). The number and proportion of women who had received osteoporosis treatment within the past 12 months was 25,860 (10.7%). The most frequent comorbidities were dementia (15,120 [6.3%]), diabetes without chronic complications (14,639 [6.1%]), and congestive heart failure (13,973 [5.8%]). Most women (173,138 [71.5%]) had received medications associated with increased risk of falls within the 12 months preceding the index fracture.

Incidence of subsequent fracture

The number of subsequent fracture events within 12 months was 16,145 and within 24 months was 25,545. The overall cumulative subsequent fracture incidence at 12 months following any index fracture was 7.1% (95% confidence interval [CI], 6.9–7.2) and at 24 months was 12.0% (95% CI, 11.8–12.1; Fig. 1a). The rate of subsequent fractures was highest in the first month following fracture (~15 fractures per 1000 patient-years) and then remained consistently elevated between 4 and 24 months at ~5 fractures/1000 patient-years (Fig. 1b).

A total of 20,811 deaths occurred within 12 months and 31,390 deaths within 24 months of the follow-up period. The numbers of competing events of death before subsequent fracture were 19,153 within 12 months and 27,331 within 24 months.

Table 1 Patient characteristics at the time of the index fracture ($N = 242,108$)

Characteristic	Value	
Mean age, years (SD)	74.0	(12.5)
Age > 70 years, n (%)	149,305	(61.7)
Mean days of hospitalization (SD) ^a	3.2	(10.8)
Mean number of physician visits (SD) ^a	1.4	(4.1)
Osteoporosis treatment experience, n (%) ^a	25,860	(10.7)
Mean number of different medications (SD) ^a	8.1	(6.2)
Glucocorticoid use, n (%) ^a	16,561	(6.8)
Assisted drug dispensing, n (%) ^a	39,444	(16.3)
Exposure to drugs associated with an increase in risk of falls, n (%) ^a	173,138	(71.5)
Secondary osteoporosis, n (%) ^b	22,546	(9.3)
Mean Charlson comorbidity index (SD) ^c	0.5	(0.9)
Charlson comorbidities, n (%)		
Cerebrovascular disease	11,601	(4.8)
Chronic pulmonary disease	12,649	(5.2)
Congestive heart failure	13,973	(5.8)
Dementia	15,120	(6.3)
Diabetes with chronic complications	4249	(1.8)
Diabetes without chronic complications	14,639	(6.1)
Hemiplegia or paraplegia	1293	(0.5)
Mild liver disease	1357	(0.6)
Moderate-to-severe liver disease	282	(0.1)
Myocardial infarction	9113	(3.8)
Peptic ulcer disease	1481	(0.6)
Peripheral vascular disease	3087	(1.3)
Renal disease	2507	(1.0)
Rheumatic disease	8969	(3.7)

SD standard deviation

^a Within the last 12 months

^b Defined according to Landfeldt et al. [41]

^c Median = 0

Risk factors for subsequent fracture

Independent risk factors for subsequent fracture within 12 and 24 months, as identified by multivariate analysis, are shown in Table 2. Higher age was an independent risk factor for subsequent fracture within 12 and 24 months, notably with HRs > 2.0 in the 70–79 years age group and HRs > 3.0 in those aged ≥ 80 years compared with those aged 50–59 years (Table 2). Index vertebral fracture was a strong independent risk factor for imminent fracture risk relative to index hip fracture (HR, 2.72; $p < 0.001$). Similar results were seen for fractures within 24 months. Following NH/NV fracture, there was an increased risk of subsequent fracture within 12 and 24 months relative to hip fracture (at 12 months: HR, 1.29; $p < 0.001$, at 24 months: HR, 1.14; $p < 0.001$). Charlson comorbidity index scores of 1 and ≥ 2 were associated with an increased risk of subsequent fractures compared with an index score of 0 (Table 2). Use of assisted drug dispensing and osteoporosis medications was also associated with an increased risk of subsequent fracture. Despite taking into account the competing risk of death, comorbidities (cerebrovascular disease, congestive heart failure, dementia, diabetes without chronic

complications, mild liver disease, renal disease, and rheumatic disease) were also predictors of subsequent fracture at 12 and 24 months (Supplementary Table S5).

Discussion

In this study, we report the incidence of a subsequent fracture within 1 and 2 years following initial fracture in women ≥ 50 years of age in Sweden by index fracture type. The highest risk of subsequent fractures was observed following a clinical vertebral fracture. In addition, we show that even when taking into account the competing risk of death, advancing age and comorbidities remain strong independent risk factors for imminent fracture. We also observed a high frequency of usage of medications known to increase fall risk in the year before the index fracture.

In the current study, the incidence of subsequent fractures within 12 months was 7.1%, increasing to 12.0% at 24 months. This is similar to a previous study of 4140 postmenopausal women performed in The Netherlands, where the absolute risk of any subsequent fracture in the year following first fracture was 6.1% [25]. Unlike the current study, the study undertaken in The Netherlands was a questionnaire study and relied on the proportion of patients who responded to the request to complete the questionnaire; this is likely to introduce bias, as patients who had suffered a new fracture could have been over-represented in the responding group. In the current study, all women in Sweden ≥ 50 years of age with a fracture during the period of study were included, thus limiting sources of possible bias.

Our data are comparable with a US study of 377,561 women, which also employed a retrospective database design [26] and where the incidence of any subsequent fracture was 10% within 1 year of initial fracture. In our study, at 12 months, the incidence of subsequent fracture was highest following index clinical vertebral fracture (16.2%). This is also consistent with the US database study, where the subsequent fracture rate following index vertebral fracture was approximately 14% at 12 months [26]. In an earlier study of women with an index hip fracture, conducted in Sweden, 15% of women re-fractured within 1 year [42]. The proportion was lower in our study; 7.4% of women with index hip fracture went on to have a fracture within the following year. This difference in finding may be due to differences in sample size, patient demographic, and analysis methods. For example, the earlier Swedish study [42] comprised 766 adult women aged > 20 years compared with the 51,904 women (≥ 50 years) with index hip fracture in the current study. Further, in the study by von Friesendorff et al., a Kaplan-Meier estimate was used to quantify fracture risk, while in our study, a cumulative incidence function was used. As we took the competing risk of death into account, the cumulative incidence function will

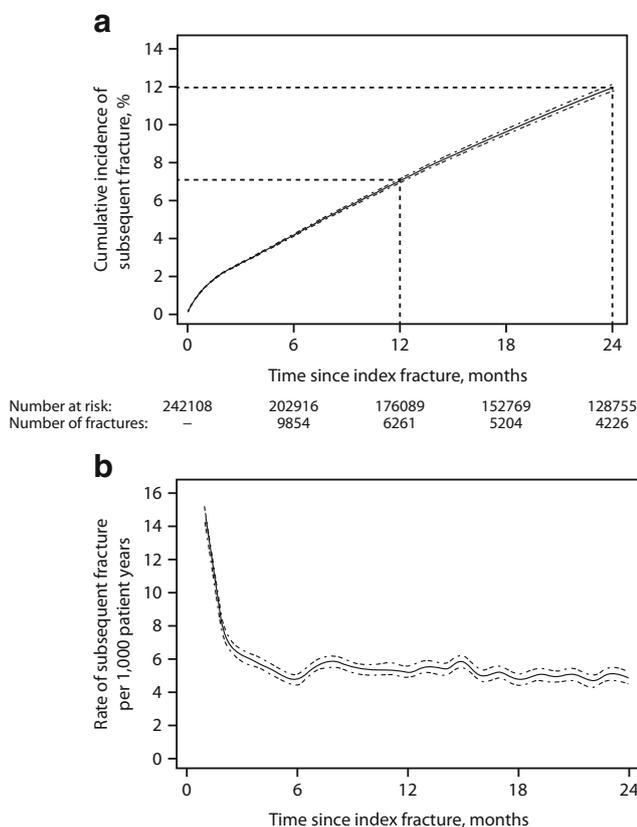


Fig. 1 **a** Cumulative incidence of any subsequent fracture (clinically diagnosed and coded fractures only were counted) during the 24 months following any index fracture. **b** Rate of any subsequent fracture (clinically diagnosed and coded fractures only were counted) during the 24 months following any index fracture

Table 2 Multivariate model of risk factors for fracture within 12 and 24 months following index fracture

Risk factor	12 months following index fracture			24 months following index fracture		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age group (reference 50–59 years)						
60–69 years	1.37	1.27–1.47	<0.001	1.32	1.25–1.40	<0.001
70–79 years	2.06	1.92–2.20	<0.001	2.04	1.93–2.15	<0.001
80–89 years	3.04	2.84–3.26	<0.001	2.99	2.84–3.16	<0.001
90+ years	3.14	2.90–3.39	<0.001	2.94	2.77–3.13	<0.001
Index fracture type (reference: hip fracture)						
NH/NV	1.29	1.23–1.34	<0.001	1.14	1.10–1.18	<0.001
Vertebral	2.72	2.58–2.88	<0.001	2.25	2.15–2.35	<0.001
Osteoporosis treatment (reference: no osteoporosis treatment) ^a	1.08	1.03–1.13	0.002	1.12	1.08–1.16	0.002
Glucocorticoid use (reference: no glucocorticoid use) ^b	1.16	1.10–1.23	<0.001	1.15	1.10–1.20	<0.001
Assisted drug dispensing (reference: no assisted drug dispensing) ^c	1.13	1.08–1.18	<0.001	1.03	0.99–1.06	0.108
Exposure to drugs that increase the risk of falls (reference: no exposure) ^d	1.22	1.16–1.27	<0.001	1.25	1.20–1.29	<0.001
CCI score (reference: CCI = 0)						
1	1.18	1.13–1.23	<0.001	1.14	1.11–1.18	<0.001
≥2	1.24	1.18–1.30	<0.001	1.16	1.11–1.20	<0.001

CCI Charlson comorbidity index, CI confidence interval, HR sub-distribution hazard ratio, NH/NV non-hip/non-vertebral

^a Osteoporosis treatment in the past 12 months, which included bisphosphonates, denosumab, strontium ranelate, raloxifene, and teriparatide

^b Glucocorticoid use in the past 12 months, defined as current exposure to oral glucocorticoids or previous exposure to oral glucocorticoids for > 3 months at a dose of prednisolone 5 mg daily or more (or equivalent doses of other glucocorticoids)

^c Assisted drug dispensing defined as use of a multi-dose drug dispensing service within the last 12 months

^d Exposure to drugs that increase the risk of falls as listed by the Swedish National Board of Health and Welfare within the past 12 months (Supplementary Table S4)

give a lower estimate than the Kaplan-Meier method if competing events are present.

In addition to the well-known elevated risk of fracture that follows a fragility fracture, we identified several independent risk factors for imminent fracture in this study. Age was an important factor; the HRs of age > 80 years compared with age 50–59 years were greater than 3.0. Age was also identified in other studies of risk factors for imminent fracture [23, 26, 43–46]. The risk of imminent fracture was doubled for every additional decade after age 50 years in a study of patients with no recent fracture [23]. A further study showed that incidence of subsequent fracture was higher with increasing age, with a HR of 1.2 per decade [44].

The risk factors identified in the current study are generally consistent with the risk factors included in the FRAX algorithm, i.e., age, rheumatic disease, and glucocorticoid use. However, we also identified other significant risk factors not included in FRAX, such as the use of a multi-dose drug dispensing service in the last 12 months, drugs that are associated with an increase in risk of falls, and specific comorbidities. Our data are consistent with the findings of the US Study of Osteoporotic Fractures (SOF), where independent predictors of any non-vertebral fracture within 1 year of follow-up included age, prior fracture, Parkinson's disease or

cerebrovascular disease, total hip T-score, prior falls, walking speed, and smoking [28]. However, in SOF, the 1-year follow-up period was not anchored to an index fragility fracture as in our study. Unlike the SOF study, in the current study, we did not capture data on falls, walking speed, or smoking status. In our study, the use of assisted drug dispensing was used as a broad proxy for dependency, frailty, medication burden, and functional and cognitive impairment, which we hypothesized would be associated with increased risk of fracture. Our findings were consistent with this hypothesis, as use of the ApoDos system was associated with a significantly increased risk of fracture.

We acknowledge that our study has some limitations. Diagnosis of fracture in this study was based on medical records, and we were not able to verify that all sustained fractures were associated with a low-trauma event. Therefore, it was not possible to make an absolute diagnosis of fragility fracture in all cases. Only ICD-10-coded clinical vertebral fractures were identified. Clinical vertebral fractures are a subset of all vertebral fractures; therefore, our numbers likely represent an underestimate of the true incidence and prevalence of vertebral fractures. While we acknowledge the limitations in the accuracy of fracture diagnoses, the diagnosis of hip fracture is expected to be more accurate than for vertebral

fractures. Hip fractures were based on the ICD-10 code S72.x. Unlike previous studies [47, 48], we did not base the identification of hip fracture on the surgical procedure code as this would exclude women who (1) died shortly after hip fracture before undergoing surgery, (2) were too frail to undergo such a procedure and/or terminally ill, and (3) patients who were transferred elsewhere for the procedure. Still, our data are likely to underestimate the incidence of subsequent fractures. We observed a higher risk of subsequent fracture in patients using osteoporosis medications, which may be explained by a potential channeling bias; this has also been observed in previous studies [49]. A history of falls is a known strong predictor of imminent future fracture [23, 28]; data on falls were not available in our study. In addition, we examine data from a single country, and findings may not be transferable to other countries or populations. However, our study also has some major strengths. It is a large inclusive sample providing data on every diagnosed fracture in Sweden during the period of investigation. The Swedish social security number, which is unique for each citizen, allows for following patients over time and allows data to be linked to other registers, i.e., the PDR and the Cause of Death Register. In addition, minimal exclusion criteria were applied; therefore, it arguably provides a more representative depiction of events in a real-world clinical setting than that reported in smaller, more selective studies. Our study provides a comprehensive account of the incidence of subsequent fractures in women with a previous fracture and the risk factors associated with subsequent fractures; it does not, however, provide an estimate of the level of fracture risk compared with a control population.

In summary, there has been extensive research estimating fracture risk over a patient's lifetime, but there is less evidence describing imminent fracture risk (within 12 and 24 months). Imminent risk of fragility fracture has been identified as an important area for further research [19, 24], provides an opportunity for rapid interventions to reduce future fracture events, and is key to the appropriate treatment of those patients at the highest risk of fracture. In such patients, to positively impact osteoporosis management, it is necessary to intervene with therapies proven to rapidly decrease fracture risk. Identifying individuals at imminent risk for fracture can be achieved through the recognition of associated risk factors, such as a recent fragility fracture and older age. In view of the current under treatment of patients at increased risk for fracture and in particular of those who have already suffered a fragility fracture, our findings highlight the need and the opportunity to put in place healthcare systems to intervene rapidly after a fracture, such as Fracture Liaison Services, or other forms of organized care intervention, linking orthopedic and emergency departments with doctors providing the longer term care of patients with fragility fractures. Indeed, the occurrence of a fragility fracture provides physicians and

medical systems with a unique opportunity to act to reduce the risk of subsequent fractures.

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Compliance with ethical standards

Ethical approval The study has been approved by the Regional Ethical Review Board in Stockholm and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. For this type of study, individual formal consent was not required.

Conflicts of interest JB, LK, OS, and GO are employed by Quantify Research, and Quantify Research was funded by UCB Pharma to conduct this study.

KEA has received lecture fees from Merck, UCB Pharma, Eli Lilly, Amgen, and Novartis.

AS has received lecture fees from Amgen and Eli Lilly.

OL has received lecture fees from Eli Lilly and Amgen.

CL and ET are employed by, and own stocks in, UCB Pharma.

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