Real-World Effectiveness of Anti-Resorptive Treatment in Patients With Incident Fragility Fractures—The STORM Cohort—A Swedish Retrospective Observational Study

Bo Freyschuss,1 Maria K. Svensson,2 Thomas Cars,2,3 Lars Lindhagen,4 Helena Johansson,5,6 and Andreas Kindmark2

1Department of Medicine, Karolinska Institute, Stockholm, Sweden
2Department of Medical Sciences, Uppsala University Hospital, Uppsala, Sweden
3Sence Research AB, Uppsala, Sweden
4Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
5Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia
6Geriatric Medicine, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

ABSTRACT
Results from real-world evidence (RWE) from the largest healthcare region in Sweden show low uptake of antiresorptive (AR) treatment, but beneficial effect in those receiving treatment, especially for the composite outcome of hip fracture or death. For RWE studies, Sweden is unique, with virtually complete coverage of electronic medical records (EMRs) and both regional and national registries, in a universal publicly funded healthcare system. To our knowledge, there is no previous RWE study evaluating the efficacy of AR treatment compared to no AR treatment after fragility fracture, including data on parenteral treatments administered in hospital settings. The Stockholm Real World Management (STORM) study cohort was established in the healthcare region of Stockholm to retrospectively assess the effectiveness of AR treatment after first fragility fracture using the regional EMR system for both hospital and primary care. Between 2012 and 2018, we identified 69,577 fragility fracture episodes among 59,078 patients, men and women, 50 years and older. Of those, 21,141 patients met inclusion and exclusion criteria (eligible cohort). From these, the final matched study cohort comprised 9840 fragility fractures (cases receiving AR treatment [n = 1640] and controls not receiving AR treatment [n = 8200]). Propensity scores were estimated using logistic regression models with AR treatment as outcome and confounders as independent variables followed by analysis using Cox proportional hazard models. Real world evidence from Sweden’s largest healthcare region, comprising a quarter of the Swedish population, show that only 10% of patients receive AR treatment within 1 year after a fragility fracture. Factors associated with not receiving treatment include having a diagnosis of cardiovascular disease. In those treated, AR have positive effects particularly on the composite of fracture and death (any fracture/death and hip fracture/death) in individuals matched for all major confounders. © 2022 The Authors. Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

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Introduction
Approximately 9 million fragility fractures occur worldwide per year.(1) In the European Union (EU), three and a half million osteoporosis-related fractures occur annually, with an estimated annual cost of 37 billion euro, and costs are estimated to rise substantially over the coming 5–10 years.(2) In Sweden, with one of the highest fracture rates in the world, 46% of women and 28% of men from the age of 50 years will have a fragility fracture during their remaining lifetime. The remaining lifetime risk of a hip fracture at 50 years of age is 23% for women and 14% for men.(3) For the individual, a hip fracture can cause loss of independence, and less than one third of patients make a full recovery. Excess mortality at 12 months after a hip fracture...
is about 30%. Although effective treatments have been available for decades, osteoporosis is still underdiagnosed and undertreated in Sweden. Registry studies conducted by national agencies in Sweden around 2010, indicated that after a fragility fracture leading to hospitalization, only around 12% of women over the age of 55 years were treated with antiresorptive agents within a year. As the national osteoporosis guidelines, effective during 2012–2018, recommended a treatment target of up to 60%–70% of patients after fragility fractures, an increased proportion of fracture patients receiving treatment over time would have been expected.

Results from randomized controlled trials (RCTs) show that the antiresorptive (AR) agents bisphosphonates and denosumab, although being different classes of AR agents, are effective in reducing bone turnover, increasing bone mineral density (BMD) and reducing fracture risk in postmenopausal women with osteoporosis. The current knowledge base has evidence of AR effects mainly from RCTs and it has become increasingly obvious that there is a lack of information on the efficacy of AR therapy in the real-world setting, especially because the clinical target populations differ substantially from the RCT populations in having abundant comorbidity and polypharmacy and lower adherence to AR therapy.

In a recent meta-analysis of RWE data in 171,623 women, the 10 studies identified had a majority of patients included on claims data, but also from pharmacy databases and one from a general practitioner (GP) database. The aggregate results showed a positive effect on fracture reduction in bisphosphonate adherent versus nonadherent patients. A limitation of claims data is that they often lack information on drug administered in the hospital setting. This is particularly a drawback in analyses of AR agents, because drugs administered in the hospital setting may constitute a significant share of all AR agents used. In analyses of treatment for osteoporosis it is therefore key to include data from both hospital and outpatient (including primary) care.

For real world evidence (RWE) studies, Sweden is unique, with the virtually complete coverage of electronic medical records (EMRs) and both regional and national registries. Sweden has a universal publicly funded healthcare system with all residents having access to healthcare. Healthcare is decentralized and administered by county councils responsible for organizing and paying for healthcare services.

To our knowledge, there is no previous RWE study evaluating the efficacy of AR treatment compared to no AR treatment after first fragility fracture, including data also on parenteral AR treatments administered in the hospital setting. We therefore established the Stockholm Real World Management (STORM) study cohort of men and women in the healthcare region of Stockholm—Sweden's largest—to retrospectively assess the real-world effectiveness of AR treatment after first fragility fracture using a large regional EMR system for both hospital and primary care.

### Patients and Methods

#### Study design

This was a noninterventional population-based cohort study comprising all patients in the Region of Stockholm that, with its 2.4 million inhabitants, accounts for 24% of the Swedish population. The STORM study cohort of men and women in the healthcare region of Stockholm was initiated with the aim to retrospectively assess the real-world effectiveness of AR treatment after first fragility fracture using a large regional EMR system for both hospital and primary care.

#### Data sources

To build a complete overview of drug exposure, covariates and outcomes we included data from the regional healthcare data warehouse of Stockholm (called VAL) and data from EMRs in the Stockholm Region. The VAL data warehouse includes information on all contacts with healthcare financed by Region Stockholm. Data for primary care are available from 2003 and for specialized outpatient care and hospitalizations from 1993. VAL also contains demographic information on patient age, sex, migration, and death. Since July 2010, information on prescription drugs dispensed in the ambulatory setting is also included. These data come from the same data source as the Swedish Prescribed Drug Register with the population coverage of over 99%.

Furthermore, we included data from the principal EMR system in the Stockholm Region covering more than 88% of the inpatient care and 75% of the outpatient care. From the EMR we included information of drugs administered in the hospital setting, clinical measurements and results from laboratory tests. All data were linked using the personal identity number unique given to each Swedish citizen, and all data were analyzed in a pseudonymized format. This study was approved by the Regional Ethical Review Board in Uppsala Sweden (Dnr: 2017/491).

#### Inclusion and exclusion criteria

For the STORM cohort, we initially included all patients, aged ≥50 years, resident in the Stockholm Region, and having their first fragility fracture (index fracture) between January 1, 2012 and December 31, 2018. The following fracture types were included: fracture of forearm, upper arm, pelvis, hip, and vertebral fractures (described in detail in section Fracture Episode Definition). Furthermore, we excluded patients ever treated with AR therapy (i.e., non-naïve) before first index fracture. AR therapy was defined as treatment with either a bisphosphonate (alendronate, risedronate, or zoledronic acid), or denosumab (which is a different class of AR drug). In order to avoid inclusion of pathological fractures due to metastases, we also excluded patients being diagnosed with malignancy. Furthermore, patients with a diagnosis of dementia before first index fracture were also excluded. Subjects without a Swedish personal identity number or residents in the Stockholm region ≤15 months during the study period were also excluded. (Anatomical Therapeutic Chemical [ATC] and International Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes for inclusion and exclusion criteria are presented in Tables S1–S9).

#### Exposures

Patients included in the study cohort were categorized into two groups: (i) patients initiating treatment with AR within 12 months after the index fracture; and (ii) patients not initiating AR treatment with AR within 12 months after the index fracture.

We defined AR therapy as having at least one pharmacy dispensation or recorded administration (for zoledronic acid) for alendronate, risedronate, zoledronic acid, or denosumab. Patients initiating AR therapy 12 months or longer after...
the index fracture were included in the control group (see section Matching Procedure).

Matching procedure

Each AR-treated patient (case) was matched to five non-AR-treated patients (controls), matching on age (maximum difference of 1 year), sex, and fracture type (see Fracture Episode Definition). Each individual was considered a valid control until becoming a case or having a new fracture after index fracture. The matching was done by randomly selecting, with replacement, five controls from the pool of valid controls; i.e., patients not yet AR-treated at the given number of days from the index fracture. This means that each patient can appear several times in the analysis database: as a case (at most once), and as a control (several times). Controls that later become cases are censored on the day of AR treatment. This procedure is similar to the one discussed in Bergman and colleagues(16) and Lu(17) with the purpose to avoid immortal time bias.

Fracture episode definition

In order to avoid misclassification of fractures (i.e., if patients have several instances of visits/admissions with fracture diagnoses recorded for the same actual fracture), we established so-called fracture episodes for the following five fracture sites (ICD-10 codes presented in Tables S1–S5):

1. Fracture of forearm (ulna and radius)
2. Fracture of upper arm
3. Hip fracture
4. Pelvic fracture
5. Vertebral fracture

The fracture episode start date was defined as the date of the patient’s first recorded fracture diagnosis (Fig. S1). If the time to a subsequent fracture diagnosis at the same site was <365 days, that fracture diagnosis was attributed to the first fracture episode. If the time to the subsequent recorded fracture diagnosis was >365 days, that diagnosis will initiate a new fracture episode. Furthermore, to be categorized as a valid fracture episode, at least one of the diagnoses recorded within the episode must be recorded by a treating physician.

Additionally, to be categorized as a fragility fracture episode, at least one of the diagnoses within the fracture episode must include an ICD-10 code of fall in the same level (ICD-10 codes presented in Supplementary Table 1).

Outcome definition

Our primary outcome was occurrence of any new fracture after index fracture. As secondary outcomes, we analyzed (i) a composite of all-cause mortality and any new fracture, (ii) hip fracture separately, (iii) a composite of all-cause mortality and hip fracture, and (iv) all-cause mortality separately. Any fracture was defined as fracture of forearm, upper arm, hip, pelvis and vertebral fractures.

Follow-up

Follow-up of patients for study outcomes began on day 0, defined as the day of initiation of AR treatment (cases) or the same number of days after index fracture as the matched AR-treated patient (controls). Cases were assumed to remain on AR treatment throughout, whereas controls were censored upon initiation of AR treatment. Follow-up ended at the first instance of death (if not the outcome), loss to follow-up (migration from Stockholm County), end of the observation period, recorded diagnosis of dementia or malignancy, or the outcome.

Covariates

In order to identify bias-minimized statistical models we used causal diagrams (http://www.dagitty.net/)18 to select confounders (Fig. S2) to be included in the statistical model. We restricted covariate selection to only include factors affecting both treatment selection and the outcome (true confounders) or factors strongly related to the outcome (potential confounders).

The result of the causal diagram process considered the following confounders to be adjusted for:

- **Demographics**: age (at index fracture), sex, sociodemographic index according to the mosaic system19
- **Comorbid conditions based on recorded ICD-10 codes (recorded within 5 years prior to index fracture)**: disorders of bone density and structure, pulmonary disease, gastrointestinal disorders, malnutrition, vitamin D deficiency, diabetes mellitus type I and type II, heart failure, cardiac arrhythmias, hypotension, syncope, and collapse, Parkinson’s disease, epilepsy, mental and behavioral disorders due to alcohol
- **Drug therapy (recorded within 15 years prior to index fracture)**: calcium/vitamin D, glucocorticoids, diuretics, estrogens, androgens
- **Laboratory measurements (most recent recorded value within 5 years prior to index fracture)**: alkaline phosphatase (ALP), 25-hydroxyvitamin D, parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), estimated glomerular filtration rate (eGFR) creatinine-based
- **Clinical measurements (most recent recorded value within 5 years prior to index fracture)**: Fracture Risk Assessment Tool (FRAX), smoking and alcohol habits, body mass index (BMI)
- **Health care utilization and frailty**: as a measure of general frailty among patients in the study cohort we included the following measures: Charlson Comorbidity Index (CCI), previous inpatient health care utilization (within 15 months prior to index fracture), number of dispensed drug classes (within 15 months prior to index fracture) and patients having their medication prepared in medication bags.

All included codes for the included covariates are described in detail in Supplementary Table 10.

Statistical analyses

Baseline characteristics are described as medians (and interquartile range) for continuous variables, or as n (%) for categorical variables. All results were presented for all patients and for patient 75 years and above. Covariate balance was assessed in the matched cohort using standardized difference. Covariates with standardized differences >0.1 were considered to have residual imbalance.20 In a specific analysis, we analyzed predictors for receiving AR treatment. This was performed in univariable Cox models with initiation of AR treatment as outcome and each covariate specified in the covariate section as exposure. Each covariate was analyzed one at a time and patients were censored at migration from Stockholm, death, or having a new fracture.

FRAX probabilities of major osteoporotic fractures were calculated for each patient from sex, age, BMI, previous fracture,
parental history of hip fracture, current smoking, long-term use of oral glucocorticoids, rheumatoid arthritis; other causes of secondary osteoporosis, and daily alcohol consumption of three or more units daily. Variables with missing information (parental history of hip fracture, BMI, current smoking, and daily alcohol consumption of three or more units daily) were imputed before calculating FRAX probabilities. For BMI, current smoking and daily alcohol consumption of three or more units daily, imputations were based on data from other individuals in the study cohort. Because the cohort did not contain any information on parental history of hip fracture, we used the cohorts Osteoporotic Fractures in Men (MrOS) study(21) and Sahlgrenska University hospital Prospective Evaluation of Risk of Bone fractures (SUPERB)(22) as reference cohorts for imputation of this variable.(23)

Missing values in the eligible cohort were imputed using multiple imputation with chained equations, as implemented in the R package mice.(24) Ten imputed datasets were created, using all identified confounders and a selection of the outcome variables as predictors. Numerical variables were imputed using predictive mean matching, and ordinal variables using proportional odds models.

Propensity scores (PS) were estimated for each imputed data set, using unconditional logistic regression with AR treatment as outcome and all confounders as independent variables (see section Covariates). From this, average treatment of the treated (ATT) weights were computed (these weights are 1.0 for treated patients). Finally, the analysis was carried out using ATT-weighted Cox proportional hazard models, adjusted for all confounders (double robust analysis).(25) Robust standard errors with patient as cluster were computed to handle both the weights and the fact that the same patient can appear several times in the matched cohort.

R statistical software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) was used for all analyses.

### Results

Study cohort, index fracture, baseline patient characteristics, and follow-up

Between 2012 and 2018, we identified 69,577 fracture episodes (forearm, upper arm, hip, pelvic, and vertebral) among 59,078 patients in Region Stockholm, 50 years and older. Of those, 33,484 were categorized as incident fragility fractures and subsequently 21,141 patients met inclusion, and not exclusion criteria (eligible cohort). From these, the final matched study cohort comprised 9840 patients with fragility fractures cases initiating

![Fig. 1. Derivation of the study cohort.](image-url)
treatment within 12 months (n = 1640) and controls (n = 8200). A flowchart of the study outline is presented in Fig. 1.

Overall, 8.8% of patients in the eligible cohort (n = 21,141) who had a fragility fracture received AR treatment within 12 months after the fracture and the most commonly prescribed AR treatment was alendronic acid (76%, Supplementary Table 14). Women generally had a higher rate of treatment, such that after 1 year, 10.4% of women and 3.7% of men were on AR treatment (Fig. S3). The proportion of patients receiving therapy increased over time, so that 3 years after fracture, an additional 5% had initiated AR treatment (Fig. S3). Significant predictors for receiving AR treatment included older age, female sex, previous hip or vertebral fractures, glucocorticoid treatment, and any ICD-coded diagnosis of bone disease. Predictors of not receiving AR treatment included; e.g., diagnosis of alcoholism, heart failure, cardiac arrhythmias, as well as treatment with diuretics (Supplementary Table 11).

Patient characteristics for the eligible and matched study cohorts are described in Table 1.(26) The average age of the eligible cohort was 72 years, and 75% were women. The distribution of index fracture types differed between age strata, with fracture of forearm being the most common overall but hip fracture dominating in the 75+ year age strata (Table 1 and Supplementary Table 12).

Compared to the eligible cohort, patients initiating AR within 12 months after first fragility fracture were similar in age but were more often female, had more often been diagnosed with disorders of bone density and structure, were more often treated with calcium and/or vitamin D, had higher FRAX estimates, were less likely to have heart failure or diuretic treatment, and were less likely to use dispensed medication bags.

Before weighting on the propensity score, we observed imbalances in eight out of 42 covariates included in the statistical model (standardized difference >0.1). After weighting on the PS, no residual imbalance was observed (Table 1).

The mean follow-up time for the outcome any fracture or the composite of any fracture and all-cause mortality was 2.7 years for patients initiating AR treatment and 2.6 years for patients without AR treatment. The corresponding number for hip fracture and the composite of hip fracture and all-cause mortality was 2.8 years per patient for patient with AR and 2.6 years for patients not treated with AR.

Outcomes Table 2 presents hazard ratios (HRs) for the primary and secondary outcomes. For the primary outcome of any fracture, the adjusted and weighted HR was 0.98 (95% confidence interval [CI], 0.77–1.25) for all ages and 0.91 (95% CI, 0.64–1.25) for the age group 75 years or older. For the composite outcome of any fracture and all-cause mortality the adjusted and weighted HR was 0.83 (95% CI, 0.69–1.00) for all ages and 0.78 (95% CI, 0.60–1.00) for 75 years or older. The same trend (HR 0.67; 95% CI, 0.50–0.89) were observed for the composite outcome of hip fracture and all-cause mortality for the age group 75 years or older. For all-cause mortality (death), the HR was 0.65 (95% CI, 0.49–0.86) for all ages, and 0.68 (95% CI, 0.49–0.95) for the age group 75 years and older.

The results are also depicted in Fig. 2 by Kaplan-Meier plots for the respective outcomes for any fractures (upper panels) or hip fractures (lower panels) and the composite outcome of fracture and all-cause mortality.

Discussion AR therapies have been shown to be effective in preventing fragility fractures in RCTS,27 in studies of insurance claims databases,28,29 and in registry studies.30 The proportion of women older than 55 years with fragility fractures over the last 10–15 years that are treated with bone-specific treatments in Sweden within 1 year after fracture has been at a rather steady low level of 14.9% during 2006–2008,31 decreasing even further to 12.0%–12.9% between 2011 and 2014.32 Real-world management studies from actual healthcare regions are less common, and even less common when spanning both primary care, specialized outpatient clinics and hospital care. In the STORM cohort, we have data available for both prescribed and administered AR therapy regardless of healthcare setting, and a long follow-up time compared to many previous RWE studies.

In the present study, we queried the EMRs and regional healthcare databases for patients sustaining fragility fractures in Stockholm, the largest healthcare region in Sweden with its 2.4 million inhabitants. Fracture liaison services (FLS) have been shown to be cost effective in preventing fractures in a number of studies,33 but the Stockholm healthcare region did not have an implemented FLS during the study period.

Actually only around 15% of patients actually received AR therapy within 3 years after index fracture (Fig. S3), although AR therapy for those eligible was the current recommendation in the different available Swedish national guidelines between 1998 and throughout the study period.36-39 This was the case despite all patients having sustained a fragility fracture and having mean FRAX values above a 20% 10-year risk of major osteoporotic fracture, a level well within the range that should be considered for AR treatment according to the concurrent guidelines.60 In the present study, after having sustained a fragility fracture, analyses showed that significant predictors for receiving AR treatment included older age, female sex, hip or vertebral fractures, glucocorticoid treatment, and diagnosed bone disease (potentially indicating having performed a dual-energy X-ray absorptiometry [DXA] scan). All of these are covariates that are included in treatment algorithms for treatment decisions, which would indicate that the algorithms “work,” although the number of patients treated is far lower than is desirable. Furthermore, patients with elevated levels of parathyroid hormone (PTH), are less likely to be on AR treatment. Other, predictors of not receiving AR treatment included; e.g., diagnosis of heart failure and alcoholism (Supplementary Table 11). This may reflect a reluctance to treat complex cases in spite of a potentially very high fracture risk. For example, an undertreatment of older patients (>80 years) has previously been shown.35

Significant risk reductions in vertebral fractures, nonvertebral fractures, and hip fractures have been well established in large randomized trials for the antiresorptive included in this study.36-39 There may be several potential explanations for having fracture endpoints resulting neutral in our study. First, there is most likely a selection bias for patients with higher fracture risk in the treated group versus the untreated. This is suggested by the higher prevalence of some important risk factors in the matched sample before weighting on the propensity score (Table 1), for example higher use of oral glucocorticoids 13% versus 9% and calcium 20% versus 14%, and a slightly higher FRAX score in the treated group. It is also logical to assume that if only approximately 10% of the fractured patients received treatment, they would to a large extent be selected based on a perceived high risk of refracture, and matching and weighting on the
### Table 1. Baseline Patient Characteristics

| Characteristic                                    | Eligible cohort | Matched cohort (unweighted) | Matched cohort (weighted on the PS) | Standardized difference |
|--------------------------------------------------|----------------|-----------------------------|-------------------------------------|-------------------------|
|                                                  |                | Fragility fractures treated with AR treatment (cases) | Fragility fractures treated with AR treatment (controls) | Fragility fractures treated with AR treatment (cases) | Fragility fractures treated with AR treatment (controls) | Standardized difference |
|                                                  |                | Standardized difference | Standardized difference | Standardized difference | Standardized difference |                     |
|                                                  |                |                            |                            |                          |                          |                     |
| **n**                                            | 21,141         | 1640                        | 8200                      | 1640                     | 8200                     |                      |
| **Demographics**                                 |                |                            |                            |                          |                          |                     |
| Age (years), median at index fracture (IQR)      | 72.0 (62.0–82.0) | 72.0 (66.0–79.0)           | 72.0 (66.0–79.0)           | N/A*                    | 72.0 (66.0–79.0)        | 72.0 (66.0–79.0)     | 0.004                 |
| **Women, %**                                     | 75.1           | 89.6                        | 89.6                      | N/A*                    | 89.6                      | 90.0                  | 0.012                 |
| SES, %                                           |                |                            |                            |                          |                          |                     |
| High                                             | 41.3           | 41.2                        | 39.0                      | 0.044                   | 41.2                      | 41.1                  | 0.002                 |
| Middle                                           | 18.7           | 16.8                        | 18.8                      | 0.054                   | 16.8                      | 16.8                  | 0.001                 |
| Low                                              | 40.0           | 42.1                        | 42.1                      | 0.002                   | 42.1                      | 42.2                  | 0.002                 |
| **Index fracture (type), %**                     |                |                            |                            |                          |                          |                     |
| Pelvic                                           | 5.3            | 4.6                         | 4.6                       | N/A*                    | 4.6                       | 4.6                   | 0.000                 |
| Hip                                              | 29.3           | 36.6                        | 36.6                      | N/A*                    | 36.6                      | 36.3                  | 0.007                 |
| Vertebral                                        | 4.0            | 5.3                         | 5.3                       | N/A*                    | 5.3                       | 5.3                   | 0.002                 |
| Upper arm                                        | 21.0           | 14.8                        | 14.8                      | N/A*                    | 14.8                      | 14.8                  | 0.002                 |
| Forearm                                          | 40.4           | 38.7                        | 38.7                      | N/A*                    | 38.7                      | 39.0                  | 0.006                 |
| **Comorbid conditions (defined by ICD codes), %**|                |                            |                            |                          |                          |                     |
| Disorders of bone density and structure          | 6.3            | 14.8                        | 7.0                       | 0.250**                 | 14.8                      | 15.1                  | 0.012                 |
| Asthma or COPD                                   | 13.6           | 15.4                        | 14.7                      | 0.018                   | 15.4                      | 15.6                  | 0.005                 |
| Gastrointestinal disorders                       | 2.8            | 3.4                         | 3.1                       | 0.012                   | 3.4                       | 3.6                   | 0.011                 |
| Malnutrition                                     | 2.6            | 2.1                         | 2.3                       | 0.017                   | 2.1                       | 2.1                   | 0.002                 |
| Vitamin D deficiency                             | 0.9            | 1.3                         | 0.7                       | 0.058                   | 1.3                       | 1.4                   | 0.015                 |
| Diabetes mellitus type I                         | 2.9            | 2.3                         | 3.0                       | 0.044                   | 2.3                       | 2.4                   | 0.006                 |
| Diabetes mellitus type II                        | 12.0           | 10.2                        | 12.2                      | 0.065                   | 10.2                      | 10.2                  | 0.000                 |
| Heart failure                                    | 10.2           | 5.6                         | 8.6                       | 0.18**                  | 5.6                       | 5.5                   | 0.003                 |
| Cardiac arrhythmia                               | 17.2           | 13.4                        | 15.2                      | 0.051                   | 13.4                      | 13.4                  | 0.002                 |
| Hypotension                                      | 3.9            | 3.0                         | 3.3                       | 0.018                   | 3.0                       | 3.0                   | 0.001                 |
| Syncope and collapse                             | 5.6            | 5.8                         | 5.5                       | 0.015                   | 5.8                       | 5.9                   | 0.004                 |
| Parkinson’s disease                              | 1.4            | 1.5                         | 1.5                       | 0.001                   | 1.5                       | 1.4                   | 0.004                 |
| Epilepsy                                         | 2.2            | 2.0                         | 2.3                       | 0.021                   | 2.0                       | 2.0                   | 0.002                 |
| Mental and behavioral disorders due to alcohol   | 5.7            | 3.1                         | 5.6                       | 0.123**                 | 3.1                       | 3.1                   | 0.002                 |
| **Drug use prior to index (defined by ATC), %**   |                |                            |                            |                          |                          |                     |
| Calcium/vitamin D                                | 13.2           | 19.8                        | 14.1                      | 0.153**                 | 19.8                      | 20.3                  | 0.016                 |
| Glucocorticoids                                  | 9.1            | 12.8                        | 8.9                       | 0.127**                 | 12.8                      | 13.0                  | 0.007                 |
| Diuretics                                        | 22.4           | 18.1                        | 22.4                      | 0.107**                 | 18.1                      | 18.1                  | 0.000                 |
| Estrogens                                        | 13.6           | 20.6                        | 17.0                      | 0.092                   | 20.6                      | 21.0                  | 0.011                 |
| Androgens                                        | 0.2            | 0.1                         | 0.2                       | 0.007                   | 0.1                       | 0.1                   | 0.004                 |

(Continues)
## Table 1. Continued

| Characteristic                              | Eligible cohort | Matched cohort (unweighted) | Matched cohort (weighted on the PS) | Standardized difference |
|---------------------------------------------|-----------------|-----------------------------|-------------------------------------|-------------------------|
|                                                   | Fragility fractures treated with AR treatment (cases) | Fragility fractures without AR treatment (controls) | Fragility fractures treated with AR treatment (cases) | Fragility fractures without AR treatment (controls) |
| Laboratory measurements, median (IQR)        |                 |                             |                                     |                         |
| Alkaline phosphatase (ALP) (μkat/L)          | 1.2 (1.0–1.5)   | 1.2 (1.0–1.5)               | 1.2 (1.0–1.5)                      | 1.2 (1.0–1.5)           |
| 25-hydroxyvitamin D (nmol/L)                 | 55.0 (37.0–78.0)| 59.0 (40.0–80.0)            | 58.0 (39.0–80.0)                   | 59.0 (40.0–80.0)        |
| Parathyroid hormone (PTH) (pmol/L)           | 6.0 (4.1–10.0)  | 4.8 (3.5–6.9)               | 4.9 (3.7–7.1)                      | 4.8 (3.5–6.9)           |
| TSH (mIE/L)                                  | 1.6 (1.0–2.3)   | 1.5 (0.9–2.2)               | 1.5 (1.0–2.3)                      | 1.5 (0.9–2.2)           |
| eGFR (mL/min)                                | 68.7 (55.0–80.7)| 71.7 (61.0–81.8)            | 71.2 (59.6–81.9)                   | 71.7 (61.0–81.8)        |
| Clinical measurements                         |                 |                             |                                     |                         |
| FRAX (10-year risk of major osteoporotic fracture), % | 16.8 (9.6–27.8) | 21.6 (13.2–31.2)            | 20.1 (12.4–29.8)                 | 21.6 (13.2–31.3)        |
| Smoking habits, %                            |                 |                             |                                     |                         |
| Yes                                         | 14.5            | 12.1                        | 14.2                                | 12.1                    |
| No                                          | 62.0            | 68.2                        | 64.8                                | 68.2                    |
| Former                                      | 23.5            | 19.6                        | 21.0                                | 19.6                    |
| Alcohol habits, %                            |                 |                             |                                     |                         |
| <1 standard drink                            | 51.1            | 48.4                        | 50.1                                | 48.4                    |
| 1–4 standard drinks                          | 30.5            | 32.8                        | 30.5                                | 32.8                    |
| 5–9 standard drinks                          | 11.7            | 12.9                        | 13.5                                | 12.9                    |
| 10+ standard drinks                          | 6.8             | 5.9                         | 6.0                                 | 5.9                     |
| BMI (kg/m²), median (IQR)                    | 24.2 (21.5–27.5)| 24.0 (21.5–26.9)            | 24.5 (21.8–27.8)                   | 24.0 (21.5–26.9)        |
| Indicators of health care utilization and frailty |                 |                             |                                     |                         |
| CCI, median (IQR)                            | 1.0 (0.0–2.0)   | 0.00 (0.00–1.00)            | 1.00 (0.00–2.00)                   | 0.00 (0.00–1.00)        |
| Number of drug classes (based on 4-digit ATC-level) prior to index fracture, median (IQR) | 6.0 (3.0–10.0) | 6.0 (3.0–11.0) | 6.0 (3.0–11.0) | 7.0 (3.0–11.0) |
| Patient with dispensed medication bags, %    | 9.3             | 4.0                         | 8.3                                 | 4.0                     |
| Previous inpatient health care utilization before index fracture, median (IQR) | 0.0 (0.0–16.0) | 2.0 (0.0–15.0) | 2.0 (0.0–16.0) | 2.0 (0.0–15.0) |

For socioeconomic status, laboratory values and clinical measurements we have missing information. The proportion of missingness is presented in Supplementary Table 13.

Baseline clinical characteristics for the eligible cohort and for the matched cohort is based on nonimputed data and imputed data, respectively.

ATC = Anatomical Therapeutic Chemical; BMI = body mass index; CCI = Charlson Comorbidity Index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; N/A = not applicable; PTH = parathyroid hormone; SES = socioeconomic status; TSH = thyroid stimulating hormone.

*The study cohort is matched by age, sex, and index fracture and therefore balanced by study design.

** Covariates with observed unbalances before weighting.

*** As a measure of comorbidity and healthcare utilization, we included the number prescribed drug classes (on a 4-digit level) before index. 

(26)
### Table 2. HRs for the Matched Study Cohort

| Outcome                        | All ages | Age 75+ |
|--------------------------------|----------|---------|
|                                | Crude HR (95% CI) | Adjusted * HR (95% CI) | Adjusted ** HR (95% CI) | Crude HR (95% CI) | Adjusted * HR (95% CI) | Adjusted ** HR (95% CI) | Events (n) |
| Any fracture***                | 1.03 (0.86–1.23) | 0.97 (0.80–1.17) | 0.98 (0.77–1.25) | 851 | 0.97 (0.75–1.25) | 0.91 (0.69–1.21) | 0.91 (0.64–1.29) | 420 |
| Any fracture/death***         | 0.79 (0.68–0.91) | 0.83 (0.71–0.96) | 0.83 (0.69–1.00) | 1577 | 0.73 (0.60–0.88) | 0.78 (0.64–0.96) | 0.78 (0.60–1.00) | 948 |
| Hip fracture                   | 0.91 (0.69–1.20) | 0.85 (0.64–1.14) | 0.88 (0.61–1.26) | 385 | 0.84 (0.59–1.20) | 0.75 (0.51–1.11) | 0.73 (0.46–1.18) | 244 |
| Hip fracture/death             | 0.66 (0.55–0.78) | 0.70 (0.58–0.85) | 0.70 (0.56–0.89) | 1165 | 0.64 (0.52–0.79) | 0.68 (0.54–0.86) | 0.67 (0.50–0.89) | 819 |
| Death                          | 0.57 (0.46–0.71) | 0.66 (0.52–0.83) | 0.65 (0.49–0.86) | 862 | 0.61 (0.46–0.78) | 0.69 (0.53–0.91) | 0.68 (0.49–0.95) | 638 |

Cl = confidence interval; HR = hazard ratio.

* Cox model adjusted for all covariates specified in the statistical model.

** Cox model adjusted for all covariates and weighted on the propensity score (double robust analysis).

*** Fracture of forearm, upper arm, hip, pelvis, and vertebral.

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Cl = confidence interval; HR = hazard ratio.

* Cox model adjusted for all covariates specified in the statistical model.

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*** Fracture of forearm, upper arm, hip, pelvis, and vertebral.

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** Cox model adjusted for all covariates specified in the statistical model.

** Cox model adjusted for all covariates and weighted on the propensity score (double robust analysis).

*** Fracture of forearm, upper arm, hip, pelvis, and vertebral.
Analysis Osteoporosis Prospective Risk Assessment study (OPRA) cohort study of 75 year old Swedish women,[51] where a subjective estimate of the biological age was shown to be predictive of future fractures and death. This factor was not captured in our study.

A strength of this study is that the STORM cohort comprises extracted and linked data from both administrative data sources and EMRs from a large well-defined region with universal access to primary, secondary and tertiary healthcare for all residents; and access to data from all those healthcare sources, allowing us to build a virtually complete overview of drug exposure, covariates, and outcomes. Furthermore, the data also includes administered doses of zoledronic acid from a majority of the healthcare regions hospitals, data which may not have been captured in previous studies based on prescribed drugs. Limitations include the risk of unmeasured confounding, a potential risk in all observational studies.

In conclusion, our results from the STORM cohort based on real world data from Sweden’s largest healthcare region comprising a quarter of the Swedish population show that only 10% of patients with fragility fractures after the age of 50 years receive antiresorptive treatment within 1 year after first fragility fracture. In the patients who are treated, AR seem to have positive effects on the composite of fracture and death (any fracture/death and hip fracture/death) and all-cause mortality, respectively, after adjustments for all major confounders. This could either be the result of a selection bias due to the selective treatment of individuals with suspected longer survival, or an actual benefit of the intervention. The observed trend toward hip fracture reduction in the oldest patients could be due to a high incidence and a relatively high treatment effect of AR on hip fractures while the smaller effect on nonvertebral fractures was insufficient to show even a trend for fracture reduction in our study.

Our hope for the future is that our findings, in combination with new Swedish guidelines for the identification and treatment of osteoporosis implemented in 2020 and 2021 will improve the osteoporosis care in Sweden as it clearly shows the need for systematic follow-up of patients after fracture.

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**Author Contributions**

Bo Freyschuss: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing-original draft, Writing-review & editing; Maria K. Svensson: Conceptualization, Investigation, Methodology, Project administration, Writing-original draft, Writing-review & editing; Thomas Cars: Conceptualization, Data curation, Formal analysis, Investigation,
Methodology, Project administration, Validation, Visualization, Writing-original draft, Writing-review & editing; Lars Lindhagen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing-original draft, Writing-review & editing; Helena Johansson: Formal analysis, Investigation, Methodology, Visualization, Writing-original draft, Writing-review & editing; Andreas Kindmark: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing-original draft, Writing-review & editing;

Conflict of Interests

BF was an employee at Amgen 2009–2016; he has served on advisory boards for Amgen, UCB, Eli Lilly, MSD, and Novartis. MKS was employed by Amgen AB when the study was performed. TC is co-founder of an independent statistical consultant company, Sence Research AB, Uppsala, which has received funding from Amgen AB for statistical analysis for this research project. LL and HJ report no potential conflicts of interest for this study. AK has served on advisory boards for Amgen, UCB, and Amicus, and has received speaker fees or is a previous recipient of research grants from Amgen, UCB, Sanofi-Genzyme, Shire-Takeda and GMPO/Orphalan.

Peer Review

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Osteoporosis: assessing the risk of fragility fracture. 2017. London, UK: (NICE Clinical Guidelines, No. 146) National Institute for Health and Care Excellence (NICE). http://www.ncbi.nlm.nih.gov/books/NBK554920/.

2. Hemlund E, Svedbom A, Hergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Arch Osteoporos. 2013;8:136.

3. Borgström F, Karlsson L, Ortsäter G, et al. Fragility fractures in Europe: burden, management and opportunities. Arch Osteoporos. 2020;15:234.

4. Abrahamsen B, van Staa T, Aries R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633-1650.

5. Socialstyrelsen. Hälsos- och sjukvård vid kroniska sjukdomar [National Board of Health and Welfare (Socialstyrelsen)]. Healthcare in chronic conditions [Internet]. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/opptna-jamforelser/2015-12-1.pdf

6. Socialstyrelsen. Nationella riktlinjer för rörelseorganens sjukdomar [National Board of Health and Welfare (Socialstyrelsen)]. Open comparisons of healthcare quality and effectiveness [Internet]. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2012-5-1.pdf

7. Eastell R, Walsh JS, Watts NB, Siris E. Bisphosphonates for postmenopausal osteoporosis. Bone. 2011;49(1):82-88.

8. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomized FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017;5(7):513-523.

9. Fardellone P, Lello S, Cano A, et al. Real-world adherence and persistence with bisphosphonate therapy in postmenopausal women: a systematic review. Clin Ther. 2019;41(8):1576-1588.

10. Ludvigsson JF, Almqvist C, Bonamy A-KE, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-136.

11. Anell A. The public-private pendulum—patient choice and equity in Sweden. N Engl J Med. 2015;372(1):1-4.

12. Cars T, Wettermark B, Löfberg R, Eriksson L, Sundström J, Lördal M. Healthcare utilisation and drug treatment in a large cohort of patients with inflammatory bowel disease. J Crohns Colitis. 2016;10(5):556-565.

13. Wettermark B, Hammar N, Fored CM, et al. The new Swedish prescribed drug register—opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-735.

14. Cars T. Real-time monitoring of healthcare interventions in routine care: effectiveness and safety of newly introduced medicines. http://uu.diva-portal.org/smash/get/diva2:1015130/FULLTEXT01.pdf

15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbohm A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-667.

16. Bergman J, Nordström A, Hommel A, Kivipelto M, Nordström P. Bisphosphonates and mortality: confounding in observational studies? Osteoporos Int. 2019;30(10):1973-1982.

17. Lu B. Propensity score matching with time-dependent covariates. Biometrics. 2005;61(3):721-728.

18. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package “dagitty.” Int J Epidemiol. 2016;45(6):1887-1894.

19. Dahlén E, Komen J, Jonsson EW, Almqvist C, Kull I, Wettermark B. Eliminated patient fee and changes in dispensing patterns of asthma medication in children—an interrupted time series analysis. Basic Clin Pharmacol Toxicol. 2019;125(4):360-369.

20. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. Pharmacoepidemiol Drug Saf. 2008;17(12):1202-1217.

21. Ohlsson C, Mellström D, Carlsson D, et al. Older men with low serum IGF-1 have an increased risk of incident fractures: the MrOS Sweden study. J Bone Miner Res. 2011;26(4):865-872.

22. Larsson B, Mellström D, Johansson L, Nilsson AG, Lorentzon M, Sundh D. Normal bone microstructure and density but worse physical function in older women treated with selective serotonin reuptake inhibitors, a cross-sectional population-based study. Calcif Tissue Int. 2018;103(3):278-288.

23. Kanis JA, Odén A, Mccloskey EV, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23(9):2239-2256.

24. Royston P, White I. Multiple imputation by chained equations (MICE): implementation in Stata. J Stat Softw. 2011;45(4):1-20.

25. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Poli Anal. 2007;15(3):199-236.

26. Brilleman SL, Salisbury C. Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study. Fam Pract. 2013;30(2):172-178.

27. Russell RGG. Bisphosphonates: the first 40 years. Bone. 2011;49(1):2-19.

28. Yusuf AA, Cummings SR, Watts NB, et al. Real-world effectiveness of osteoporosis therapies for fracture reduction in post-menopausal women. Arch Osteoporos. 2018;13(1):33.

29. Tripko-Shkolnik L, Fund N, Rohuch V, Chodick G, Shalev V, Goldstein L. Fracture incidence after denosumab discontinuation: real-world data from a large healthcare provider. Bone. 2020;130:115150.
30. Bergman J, Nordström A, Nordström P. Bisphosphonate use after clinical fracture and risk of new fracture. Osteoporos Int. 2018;29(4):937-945.

31. Socialstyrelsen. Öppna jämförelser av hälso- och sjukvårdens kvalitet och effektivitet (in Swedish) [National Board of Health and Welfare (Socialstyrelsen). Open comparisons of healthcare quality and effectiveness] [Internet]. 2009. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/oppna-jamforelser/2009-11-2.pdf

32. Sveriges Kommuner och Regioner. Vården i siffror (In Swedish) [Swedish Association of Local Authorities and Regions. Healthcare in figures.] [Internet]. https://vardenisiffror.se/

33. Turner DA, Khioe RFS, Shepstone L, et al. The cost-effectiveness of screening in the community to reduce osteoporotic fractures in older women in the UK: economic evaluation of the SCOOP study. J Bone Miner Res. 2018;33(5):845-851.

34. Läkemedelsverket. Behandling av osteoporos – Behandlingsrekom- mendation. Information från Läkemedelsverket (In Swedish) [Swedish Medical Products Agency. Treatment of osteoporosis - Recommendations. Information from the Medical Products Agency] [Internet]. Report No.: 2007: (18)4. www.lakemedelsverket.se

35. Feldstein A, Elmer PJ, Orwoll E, Herson M, Hillier T. Bone mineral density measurement and treatment for osteoporosis in older individuals with fractures: a gap in evidence-based practice guideline implementation. Arch Intern Med. 2003;163(18):2165-2172.

36. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008;Jan 23(1):CD001155.

37. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008;Jan 23(1):CD004523.

38. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-1822.

39. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-765.

40. Brozek W, Reichardt B, Zwerina J, Dimaï HP, Klaushofer K, Zwettler E. Antiresorptive therapy and risk of mortality and refracture in osteoporosis-related hip fracture: a nationwide study. Osteoporos Int. 2016;27(1):387-396.

41. Axelsson KF, Wallander M, Johansson H, Lundh D, Lorentzon M. Hip fracture risk and safety with alendronate treatment in the oldest-old. J Intern Med. 2017;282(6):546-559.

42. Landfeldt E, Lundkvist J, Ström O. The societal burden of poor persistence to treatment of osteoporosis in Sweden. Bone. 2011;48(2):380-388.

43. Ramchand SK, Seeman E. Advances and unmet needs in the thera- peutics of bone fragility. Front Endocrinol. 2018;9:505.

44. Ström O, Lauppe R, Ljunggren Ö, et al. Real-world effectiveness of osteoporosis treatment in the oldest old. Osteoporos Int. 2020;31(8):1525-1533.

45. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357(18):1799-1809.

46. Reid IR, Horne AM, Milhov B, et al. Fracture prevention with Zoledro- nate in older women with osteopenia. N Engl J Med. 2018;379(25):2407-2416.

47. Cummings SR, Lui L-Y, Eastell R, Allen IE. Association between drug treatments for patients with osteoporosis and overall mortality rates: a meta-analysis. JAMA Intern Med. 2019;179(11):1491-1500.

48. Colón-Emeric CS, Mesenbrink P, Lyles KW, et al. Potential mediators of the mortality reduction with zoledronic acid after hip fracture. J Bone Miner Res. 2010;25(1):91-97.

49. Casula M, Olmastroni E, Galimberti F, et al. Association between the cumulative exposure to bisphosphonates and hospitalization for atherosclerotic cardiovascular events: a population-based study. Atherosclerosis. 2020;301:1-7.

50. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015;386(10001):1353-1361.

51. Gerdhem P, Ringsberg K, Akesson K, Obstani KJ. Just one look, and fractures and death can be predicted in elderly ambulatory women. Gerontology. 2004;50(5):309-314.