ORIGINAL ARTICLE

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

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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).

KEY WORDS: OSTEOPOROSIS; FRACTURE PREVENTION; ANTIRESORPTIVES; GENERAL POPULATION; REAL WORLD EFFECTIVENESS

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

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is about 30%.[4] 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 anti-resorptive agents within a year.[5] 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.[6]

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.[7,8] 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,[9] 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.[10] Sweden has a universal publicly funded healthcare system with all residents having access to healthcare.[11] 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)[12] 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%.[13]

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.[14] 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,[15] 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 6).

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 (emigration 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 system[19]
- *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 patient 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

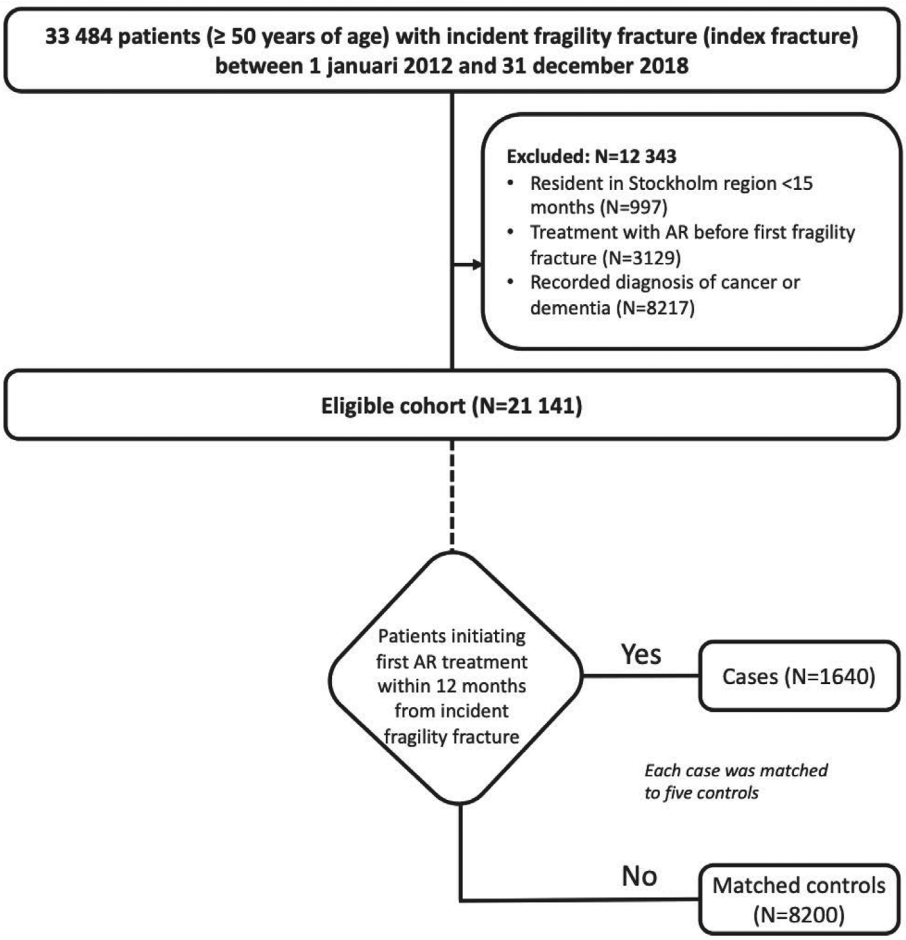

Fig. 1. Derivation of the study cohort.

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, 0.64–1.29) 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.[6,34] 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.[6]

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 antiresorptives 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)		
		Fragility fractures treated with AR treatment (cases)	Fragility fractures without AR treatment (controls)	Standardized difference	Fragility fractures treated with AR treatment (cases)	Fragility fractures without AR treatment (controls)	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	0.118**	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)		Standardized difference	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)	0.029	1.2 (1.0–1.5)	1.2 (1.0–1.5)	0.001
25-hydroxyvitamin D (nmol/L)	55.0 (37.0–78.0)	59.0 (40.0–80.0)	58.0 (39.0–80.0)	0.034	59.0 (40.0–80.0)	59.0 (41.0–81.0)	0.006
Parathyroid hormone (PTH) (pmol/L)	6.0 (4.1–10.0)	4.8 (3.5–6.9)	4.9 (3.7–7.1)	0.035	4.8 (3.5–6.9)	4.9 (3.6–7.0)	0.005
(TSH) (mIE/L)	1.6 (1.0–2.3)	1.5 (0.9–2.2)	1.5 (1.0–2.3)	0.039	1.5 (0.9–2.2)	1.5 (0.9–2.2)	0.000
eGFR (mL/min)	68.7 (55.0–80.7)	71.7 (61.0–81.8)	71.2 (59.6–81.9)	0.054	71.7 (61.0–81.8)	71.7 (61.5–81.8)	0.000
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)	0.091	21.6 (13.2–31.3)	21.7 (13.22–31.7)	0.004
Smoking habits, %							
Yes	14.5	12.1	14.2	0.062	12.1	12.2	0.002
No	62.0	68.2	64.8	0.073	68.2	68.2	0.000
Former	23.5	19.6	21.0	0.034	19.6	19.6	0.001
Alcohol habits, %							
<1 standard drink	51.1	48.4	50.1	0.033	48.4	48.4	0.001
1–4 standard drinks	30.5	32.8	30.5	0.051	32.8	32.9	0.003
5–9 standard drinks	11.7	12.9	13.5	0.018	12.9	12.8	0.003
10+ standard drinks	6.8	5.9	6.0	0.005	5.9	5.9	0.002
BMI (kg/m^2), median (IQR)	24.2 (21.5–27.5)	24.0 (21.5–26.9)	24.5 (21.8–27.8)	0.120**	24.0 (21.5–26.9)	24.1 (21.5–27.1)	0.000
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)	0.086	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.003
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)	0.031	6.0 (3.0–11.0)	7.0 (3.0–11.0)	0.008
Patient with dispensed medication bags, %	9.3	4.0	8.3	0.183**	4.0	4.0	0.001
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)	0.095	2.0 (0.0–15.0)	2.0 (0.0–15.0)	0.004

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)	Weighted and adjusted** HR (95% CI)	Events (*n*)	Crude HR (95% CI)	Adjusted* HR (95% CI)	Weighted and 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 (0.48–0.78)	0.69 (0.53–0.91)	0.68 (0.49–0.95)	638

CI = 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.

propensity score is unlikely to completely adjust for all differences between the groups. That individuals with the highest risk of refracture are selected for treatment by physicians is supported by a by an Austrian registry study[40] and a national Swedish registry study[30] comparing fractured individuals matched by fracture site, age, and sex. In the Swedish study the group receiving treatment had a higher fracture incidence than the untreated group before the index fracture and the first 6 months after receiving treatment. But this difference gradually disappeared, and 18 months after treatment initiation the fracture incidence in the AR-treated group and the untreated group were similar, suggesting a gradual onset of treatment effect. A gradual onset of treatment effect was observed also in a large registry study in the United States.[28] Another Swedish registry study investigated hip fracture incidence in patients over 80 years after an index fracture, using propensity score matching. A lower incidence of hip fractures was shown in the alendronate treated group versus the untreated.[41] In that study individuals in the treated group had to have at least 3 months of treatment before inclusion in the study. In the present study all cases were included day 1 after treatment initiation. Thus, second, a gradual onset of the treatment effect, especially for nonvertebral fractures that constituted about 95% of the fractures in the study, may partly explain the absence of a significant treatment effect of AR on fracture. Third, we had a very conservative approach for categorizing fractures in order to minimize the risk of erroneous diagnoses and may thereby have reduced the actual fracture incidence somewhat, thus decreasing the statistical power.

An additional explanation of the neutral effect on the primary outcome of all fractures may be a low persistence to AR treatment. Other Swedish studies have shown a persistence in the order of 50% 1 year after treatment initiation and as low as 20% after 3 years.[42] We did observe a trend for reduction of hip fractures in the AR group versus the control group (HR 0.88; 95% CI, 0.61–1.26). The observed tendency of an effect solely for hip fractures in the 75+ year-old cohort may be due to a relatively high yearly risk of hip fracture (4%) and the larger effect size with relative risk reduction (RRRs) in the order of 40% observed for AR treatment on hip fractures versus RRRs around or below 20% for nonvertebral fractures other than hip fractures in clinical trials of the antiresorptives included in this study.[43] Unfortunately, vertebral fractures with the highest clinically documented effect size of AR treatment are most likely severely underdiagnosed in our study, as in many other RWE studies, and cannot be used as a single outcome. The effect was larger in the composite measure of fracture (hip fracture) and all-cause mortality. Furthermore, we observed a lower all-cause mortality in the AR-treated group. A reduction in mortality has been seen in previous Swedish registry studies,[41,44] and furthermore in one RCT of bisphosphonates in patients with osteoporosis[45] and one study in patients with osteopenia.[46] Controversy still exists, however, with a recent meta-analysis showing no reduction in overall mortality rates in bisphosphonate-treated patients versus placebo-treated.[47] Effects of bisphosphonate treatment on mortality have been suggested to be due to a lower rate of cardiovascular diseases[48,49] and malignancies,[50] and different plausible underlying mechanisms have been suggested. Due to the available data, our study has been able to correct for a large number of predefined confounders and covariates (Fig. S2) that have not been accounted for in previous studies. In spite of this our results could be at least partly due to selection bias, for example the ''perceived biological age effect''—a phenomenon seen in the Observational Pharmaco-Epidemiology Research &

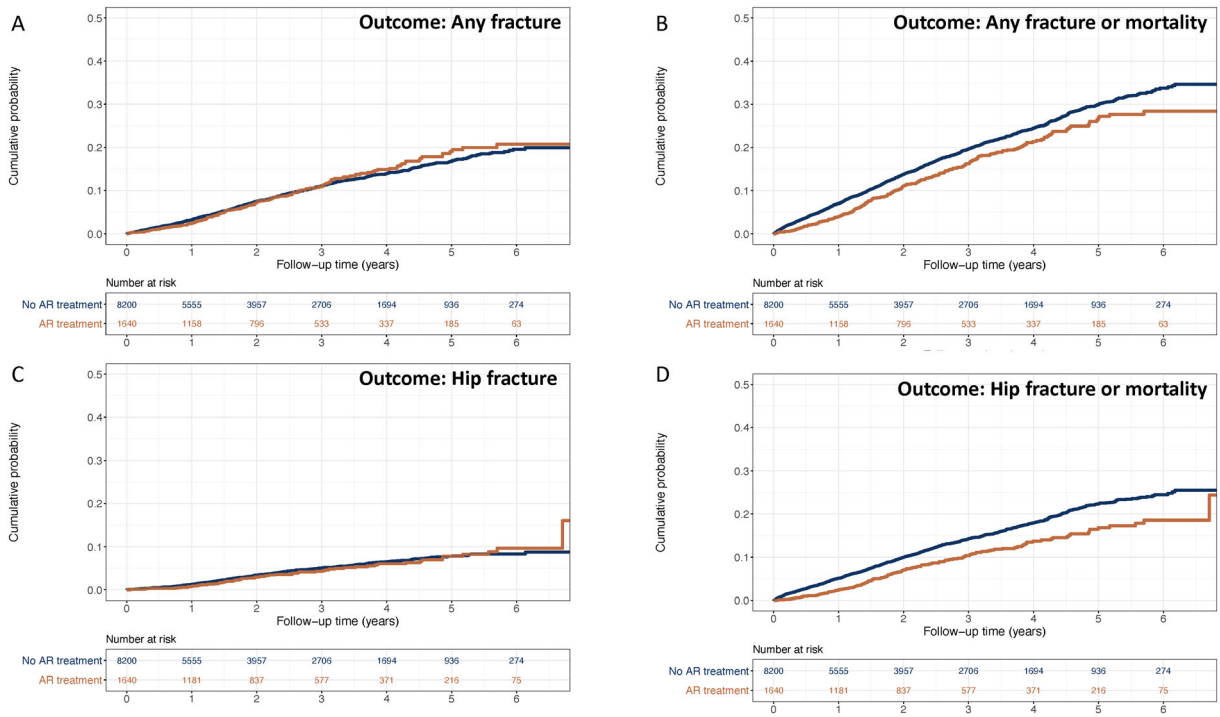

Fig. 2. The results are also depicted in Fig. 2 by Kaplan-Meier plots for the respective outcomes for the cumulative probability of (*A*) any fracture, (*B*) composite of any fracture and mortality, (*C*) hip fracture, and (*D*) composite of hip fracture and mortality after index fracture.

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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Authors' roles: BF, MKS, TC, LL, HJ, and AK designed the study. TC, LL, and HJ collected the data. BF, MKS, TC, LL, HJ, and AK analyzed and/or interpreted the data. TC, LL, and AK drafted the manuscript. Content revisions were provided by BF, MKS, TC, LL, HJ, and AK. All authors approved the final version. TC, LL, HJ, and AK take responsibility for the integrity of the data analysis.

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.

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