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ORIGINAL ARTICLE

Bisphosphonate utilization across the spectrum of eGFR

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Abstract

Summary Bisphosphonates are the most common treatment for osteoporosis but there are concerns regarding its use in CKD. We evaluated the frequency of BSP by eGFR categories among patients with osteoporosis from two healthcare systems. Our results show that 56% of patients were treated, with reduced odds in those with lower eGFR.

Introduction Osteoporosis is common in patients with chronic kidney disease (CKD). Bisphosphonates (BSP) are the most common treatment but there are concerns regarding its efficacy and toxicity in CKD. We evaluated the frequency of BSP use by level of estimated glomerular filtration rate (eGFR) in patients with osteoporosis.

Methods We assessed BSP use in patients with incident osteoporosis from the SCREAM-Cohort, Stockholm-Sweden, and Geisinger Healthcare, PA, USA. Osteoporosis was defined as the first encountered ICD diagnosis, and BSP use was defined as the dispensation or prescription of any BSP from 6 months prior to 3 years after the diagnosis. Multinomial logistic regression was used to account for the competing risk of death.

Results A total of 15,719 women and 3011 men in SCREAM and 17,325 women and 3568 men in Geisinger with incident osteoporosis were included. Overall, 56% of individuals used BSP in both studies, with a higher proportion in women. After adjustments, the odds of BSP was lower across lower eGFR in SCREAM, ranging from 0.90 (0.81–0.99) for eGFR 75–89 mL/min/1.73m^2 to 0.56 (0.46–0.68) for eGFR 30–44 mL/min/1.73m^2 in women and from 0.72 (0.54–0.97) for eGFR of 60–74 to 0.42 (0.25–0.70) for eGFR 30–44 mL/min/1.73m^2 in men. In Geisinger, odds were lower for eGFR < 30 mL/min/1.73m^2 in both sexes and the frequency of BSP use dropped over time.

Conclusion In the two healthcare systems, approximately half of the people diagnosed with osteoporosis received BSP. Practices of prescription in relation to eGFR varied, but those with lower eGFR were less likely to receive BSP.

Keywords Osteoporosis · CKD · Bisphosphonates · eGFR · CKD-MBD

Introduction

Osteoporosis is a common condition among people aged more than 50 years, affecting 10.2 million adults in the USA alone in 2010 [1], and associated with increased risk of fractures [2–5]. Fractures are independently associated with an increased short- and long-term risk of mortality as well as a high number of disability-adjusted life-years [6–8]. Prevention and

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treatment of osteoporosis are important not only for reducing the incidence of fractures but also for reducing fracture-associated morbidity and mortality. Bisphosphonates (BSP) are the first-line treatment most commonly prescribed for osteoporosis.

Chronic kidney disease (CKD) is a frequent comorbid condition among people with osteoporosis and independently associated with the risk of fracture [9–13]. There are concerns regarding the use of BSP in CKD, including the induction of low turnover disease, increased risk of atypical fractures, and increased risk of kidney, gastrointestinal, and other side effects [14, 15]. As such, the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline on Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) recommends BSP use for patients with eGFR > 30 mL/min/1.73 m^2 with no evidence of CKD-MBD and at high risk of fractures [16]. However, it is not known if these recommendations are being followed in the clinical practice. In addition, in 2010, the Food and Drug Administration (FDA) released a Drug Safety Communication about the risk of atypical fractures with BSP, particularly with prolonged use [17], a warning that has been associated with a change in osteoporosis drug utilization, at least in the patients insured by Medicaid [18].

The aim of this study was to evaluate the frequency of BSP use among patients with osteoporosis across the spectrum of eGFR. For this purpose, we used data from two large healthcare systems: the SCREAM (Stockholm CREAtinine Measurements) Cohort, collecting healthcare practice from the Stockholm region, Sweden, and Geisinger, a health system serving central and northeast PA, USA.

Methods

Study populations

SCREAM is a healthcare extraction of all patients undergoing creatinine testing in Stockholm healthcare between 2006 to 2012, with a cross-link to several national data sources, including the National Population Registry, National Renal Registry, and National Prescribed Drug Registry, among others [19]. Geisinger is a large, integrated healthcare system that serves more than 3 million residents in central and northeast PA, USA. Deidentified patient data from inpatient and outpatient encounters from 2006 up to February 29, 2016, were used in this analysis. The use of data for this study was approved by the Stockholm Ethics Review Board, the Geisinger Medical Center Institutional Review Board, and the Johns Hopkins Institutional Review Board.

In both healthcare systems, inclusion criteria were the presence of incident osteoporosis defined as the first-encountered ICD code for osteoporosis (Supplementary Table 1) in those aged 18 years or more, along with availability of at least one outpatient serum creatinine up to 1 year prior to osteoporosis diagnosis in SCREAM and 18 months prior to osteoporosis diagnosis in Geisinger. In SCREAM, ICD-10 diagnoses were available for all patients since 1997, while in Geisinger, ICD codes were available from the point of patient entry into the healthcare system. The date of the first diagnosis of osteoporosis defined the baseline. In SCREAM, from 2006 to 2012, 23,274 incident osteoporosis cases were identified. A total of 4544 were excluded due to missing creatinine, renal transplantation, or Paget's disease, leaving 18,730 individuals for analysis (Supplementary Fig. 1). In Geisinger, from 2006 to 2016, 28,274 incident osteoporosis cases were identified. A total of 7381 were excluded due to renal transplantation, Paget's disease, age < 18 years or missing creatinine, age, sex, and race, leaving 20,893 individuals for analysis (Supplementary Fig. 1).

Outcome and covariate definitions

"BSP use" was ascertained as either prevalent (6 months prior to baseline) or incident use (up to 3 years following the diagnosis of osteoporosis), assessed by electronic prescription (Geisinger) or dispensations (SCREAM, ATC codes provided in Supplementary Table 2) of any class of BSP. Data for individual BSPs was also obtained using the same definitions above. In order to account for the competing risk of mortality, events of death within 3 years after osteoporosis diagnosis (but not after BSP treatment) were also computed. In SCREAM, the date of death was obtained from the Swedish Death register, with complete national coverage and no loss to follow-up. In Geisinger, the date of death is ascertained by linkage to the Social Security Death Index.

We calculated eGFR using outpatient creatinine measurements at baseline and the CKD-EPI equation [20], and participants were classified into 9 categories considering eGFR and dialysis status as follows: dialysis, ≤ 29, 30–44, 45–59, 60–74, 75–89, 90–104, 105–119, and ≥ 120 mL/min/1.73 m^2. Comorbid conditions (cardiovascular disease, heart failure, hypertension, diabetes, rheumatoid arthritis, multiple myeloma, fractures, and prostate, breast, and colon and rectum cancer) were defined by ICD codes (Supplementary Table 1) since 1997 in SCREAM or since patient entry in Geisinger Healthcare up to baseline date. Age, sex, self-reported race, smoking status, and body mass index (BMI) were captured as the closest available information up to 1 year prior to baseline. Race, BMI, and smoking were available only in Geisinger. The Geisinger cohort was also split into two time periods (2006–2011 and 2012–2016), in order to assess potential changes in the pattern of prescription over time. Medication use at baseline defined as prescription or dispensation up to 1 year prior to baseline was ascertained for injectables and oral corticosteroids, selective estrogen receptor modulators

(SERMs), non-topical hormone replacement therapy (HRT, only in Geisinger), denosumab, calcium, and vitamin D2/D3 (ATC codes used in SCREAM in Supplementary Table 2).

Statistical analysis

All analyses were performed separately for men and women. We compared baseline characteristics of participants according to baseline eGFR categories. We calculated the frequency of BSP use (for any BSP and for each individual drug) overall and by eGFR categories in the two cohorts. Lastly, we performed unadjusted and adjusted multinomial logistic regression models for the occurrence of BSP use and death, using patients who did not receive BSP as the reference group. We used the GFR category of 90–104 mL/min/1.73 m^2 as the reference group as we have previously used as it allows risk to be considered at higher and lower GFR. Higher values of eGFR are prone to overestimation of GFR related to misclassification bias by creatinine-based equations [21, 22]. Analyses were done using the R software (http://www.R-project.org) and Stata MP 14 in SCREAM and Geisinger, respectively.

Results

In Table 1, baseline characteristics by sex are shown in SCREAM and Geisinger. In SCREAM, the mean age was 72 and 66 years in women and men, respectively. A history of fracture at any site was present in 42% of women and in 35% of men, while a history of femoral and lumbar spine fractures was present in 12% in men and women. In Geisinger, the mean age was 70 and 71 years in women and men, respectively. History of fractures was less frequent than in SCREAM: fractures at any site were present in 13% of women and 22% of men, while femoral and lumbar spine fractures were present in 4% of women and 11% of men. Hormone replacement therapy was prescribed in 23% of women in Geisinger at baseline (information not available in SCREAM). Corticosteroid was used by 40% of women and 55% of men in Geisinger and in 31% of women and 37% of men in SCREAM. Baseline features according to eGFR categories in SCREAM and Geisinger are shown in Supplementary Tables 3 and 4. As expected, patients with lower eGFR were older, with higher frequencies of diabetes, hypertension, CVD, and heart failure. In addition, patients in the lower eGFR categories also presented higher rates of history of fractures in both studies.

Table 2 displays the prevalence rates of BSP use overall and according to sex and eGFR categories. The overall prevalence rate was 56% in both SCREAM and Geisinger. Women had a higher rate of BSP use in comparison to men (58% vs. 41% in SCREAM, and 57% vs. 48% in Geisinger, $p < 0.001$ for both). In SCREAM, rates were lower for those with eGFR < 44 mL/min/1.73 m^2 and for those with eGFR > 105 mL/min/1.73 m^2 in both sexes. In Geisinger, a similar pattern was observed, with lower rates for those with eGFR < 30 mL/min/1.73 m^2 and for those with eGFR > 105 mL/min/1.73 m^2 in both sexes. Those not receiving BSP were younger and had higher BMI and less comorbidities (Tables 3 and 4). In both studies, there was a similar distribution of specific BSP agents used (Supplementary Table 5).

In Geisinger, the prevalence rate of BSP use within 3 years of incident osteoporosis was significantly lower in the 2012–2016 cohort in comparison to the 2006–2011 cohort (Supplementary Table 6), with values decreasing from 60 to 47% from 2006 to 2011 to 2012–2016 overall, and from 51 to 42% and 62 to 48% in men and women, respectively (all p-values < 0.001). In both time periods, BSP use frequency was lower in those with eGFR < 30 mL/min/1.73 m^2 and eGFR > 105 mL/min/1.73 m^2.

Figure 1 shows adjusted multinomial logistic regression models on the risk of BSP use (full models available in Supplementary Table 7). In SCREAM, after adjustment for age and other confounders, there were lower odds of BSP use with lower eGFR. In women, the odds of BSP lowered from 0.90 (95%CI 0.81–0.99) for those with eGFR 75–89 mL/min/1.73 m^2 to 0.56 (95%CI 0.46–0.68) for those with eGFR of 30–44 mL/min/1.73 m^2. In men, a similar pattern was observed, with odds of BSP use of 0.72 (95%CI 0.54–0.97) for those with eGFR 60–74 mL/min/1.73 m^2 and of 0.42 (0.25–0.70) for eGFR of 30–44 mL/min/1.73 m^2. In Geisinger, the odds of prescription were significantly lower for those with an eGFR < 30 mL/min/1.73 m^2 (OR 0.54, 95%CI 0.42–0.69 in women and of 0.27, 95%CI 0.13–0.56 in men). In both studies, in women, the odds of BSP use was also lower for eGFR categories > 105 mL/min/1.73 m^2 compared to those with 90–104 mL/min/1.73 m^2. In Geisinger, results were consistent even after repeating the multivariable model without including BMI and smoking as covariates, variables with missing data.

In addition to eGFR, in SCREAM, age, history of fractures at any site, breast cancer, hypertension (women), and baseline dispensation of corticosteroids (women only) and calcium were positively associated with the odds of BSP use, whereas baseline dispensation of SERMs and denosumab were negatively associated with the odds of BSP use. In Geisinger, age, current smoking (women), RA, calcium, vitamin D2/D3 showed positive associations, whereas time-period (lower odds for the 2012–2016 cohort in relation to the 2006–2011 cohort), black race, BMI, and baseline denosumab and SERMs were inversely related to the odds of BSP use (Table 5).

Table 1 Baseline characteristics for women and men with incident osteoporosis in SCREAM and Geisinger

	SCREAM		Geisinger	
	Women $n = 15,719$	Men $n = 3011$	Women $n = 17,325$	Men $n = 3568$
Age (years)	72 (62, 81)	66 (55, 78)	70 (62, 79)	71 (60, 80)
Race (white)	–	–	17,018 (98%)	3512 (98%)
BMI (kg/m^2)	–	–	28 (24, 32)	28 (24, 31)
Smoking (current)	–	–	2219 (13%)	557 (16%)
eGFR				
Dialysis	35 (0.2%)	58 (1.9%)	74 (0.4%)	42 (1.2%)
≤ 29	274 (1.7%)	177 (5.9%)	391 (2.3%)	55 (1.5%)
30–44	804 (5.1%)	122 (4.1%)	1345 (7.8%)	250 (7.0%)
45–59	1863 (11.9%)	266 (8.8%)	2824 (16.3%)	528 (14.8%)
60–74	3240 (20.6%)	442 (14.7%)	4084 (23.5%)	740 (20.7%)
75–89	5009 (31.9%)	773 (25.7%)	4525 (26.1%)	940 (26.3%)
90–104	3534 (22.5%)	744 (24.7%)	3397 (19.6%)	692 (19.4%)
105–119	728 (4.6%)	286 (9.5%)	552 (3.2%)	230 (6.5%)
≥ 120	232 (1.5%)	143 (4.7%)	133 (0.8%)	91 (2.6%)
Diabetes mellitus	1622 (10%)	563 (19%)	3749 (22%)	934 (26%)
Hypertension	7175 (46%)	1245 (41%)	10,874 (63%)	2301 (64%)
CVD	3888 (25%)	936 (31%)	5076 (29%)	1684 (47%)
Heart failure	1830 (12%)	497 (17%)	1373 (8%)	514 (14%)
RA	1402 (9%)	271 (9%)	854 (5%)	254 (7%)
Fractures (lumbar, femur)*	1892 (12%)	371 (12%)	702 (4%)	383 (11%)
Fracture, any site	6679 (42%)	1043 (35%)	2182 (13%)	789 (22%)
MM	72 (0.5%)	34 (1%)	42 (0%)	43 (1%)
Breast cancer	1431 (9%)	–	1192 (7%)	–
Prostate cancer	–	281 (9%)	–	400 (11%)
Colon and rectum cancer	217 (1%)	39 (1%)	253 (1%)	77 (2%)
Corticosteroids	4889 (31%)	1116 (37%)	6861 (40%)	1971 (55%)
HRT		–	3987 (23%)	–
SERMs	476 (3%)	–	724 (4%)	–
Calcium	9774 (62%)	1429 (47%)	8645 (50%)	1166 (33%)
Vitamin D2/D3	9545 (61%)	1259 (42%)	9747 (56%)	1712 (48%)
Denosumab	28 (0.2%)	2 (0.1%)	58 (0%)	7 (0%)

Median, P25, and P75 for continuous variables and *n*/% for categorical ones. There were 1797 and 785 missing values for BMI and smoking, respectively, in Geisinger

RA, rheumatoid arthritis; *MM*, multiple myeloma; *HRT*, hormone replacement therapy; *SERMs*, selective estrogen receptor modulators

*Lumbar spine and femoral fractures only

Discussion

In the present analysis, we aimed to evaluate the frequency of BSP use, according to eGFR categories among patients with osteoporosis from two large healthcare systems. The analysis showed that BSP was used by approximately half of the patients, and patients with lower eGFR were less likely to receive BSP. There are implications of these findings for the care of osteoporosis in the general population and for those with CKD.

Our findings suggest there may be sub-optimal treatment of osteoporosis in the general population. In both systems, BSP was prescribed only to approximately half of the patients, with a greater proportion of women being assigned to treatment in comparison to men. In SCREAM, regardless of a higher percentage of people reporting previous history of fractures, similar rates of BSP use were observed and were seen in the two studies. In both systems, the frequency of calcium and vitamin D use (ranging from 33 to 62% for calcium and from 42 to 61% for vitamin D in women and men from the 2 cohorts) was

Table 2 Frequency of BSP use in patients with incident osteoporosis in SCREAM and Geisinger overall and according to eGFR categories and sex

eGFR*	SCREAM 2006–2012			Geisinger 2006–2016		
	All	Men	Women	All	Men	Women
All	10,395/18730 (56%)	1237/3011 (41%)	9158/15719 (58%)	11,649/20893 (56%)	1702/3568 (48%)	9947/17325 (57%)
Dialysis	1/93 (1%)	0/58 (0%)	1/35 (3%)	18/116 (16%)	6/42 (14%)	12/74 (16%)
≤ 29	91/451 (20%)	13/177 (7%)	78/274 (29%)	170/446 (38%)	11/55 (20%)	159/391 (41%)
30–44	433/926 (47%)	39/122 (32%)	394/804 (49%)	835/1595 (52%)	114/250 (46%)	721/1345 (54%)
45–59	1180/2129 (55%)	124/266 (47%)	1056/1863 (57%)	1961/3352 (59%)	262/528 (50%)	1699/2824 (60%)
60–74	2248/3682 (61%)	213/442 (48%)	2035/3240 (63%)	2845/4824 (59%)	397/740 (54%)	2448/4084 (60%)
75–89	3537/5782 (61%)	390/773 (51%)	3147/5009 (63%)	3160/5465 (58%)	497/940 (53%)	2663/4525 (59%)
90–104	2507/4278 (59%)	343/744 (46%)	2164/3534 (61%)	2255/4089 (55%)	313/692 (45%)	1942/3397 (57%)
105–119	351/1014 (35%)	92/286 (32%)	259/728 (36%)	333/782 (43%)	77/230 (33%)	256/552 (46%)
≥ 120	47/375 (13%)	23/143 (16%)	24/232 (10%)	72/224 (32%)	25/91 (27%)	47/133 (35%)

Proportion (numerator is absolute number of participants with BSP use, denominator is total number of participants in that category) and % of participants using BSP

*eGFR categories, as mL/min/1.73 m^2

Table 3 Baseline characteristics according to the occurrence of BSP use or death in SCREAM

	Women				Men			
	No BSP $n = 5505$	BSP $n = 9158$	Death $n = 1056$	p value	No BSP $n = 1392$	BSP $n = 1237$	Death $n = 382$	p value
Age (years)	67 (55, 80)	73 (65, 80)	85 (79, 91)	< 0.01	60 (45, 70)	71 (61, 79)	79 (65, 86)	< 0.01
eGFR				<0.01				< 0.01
Dialysis	28 (1)	1 (0)	6 (1)		47 (3)	0 (0)	11 (3)	
≤ 29	114 (2)	78 (1)	82 (8)		124 (9)	13 (1)	40 (10)	
30–44	250 (5)	394 (4)	160 (15)		43 (3)	39 (3)	40 (10)	
45–59	577 (10)	1056 (12)	230 (22)		94 (7)	124 (10)	48 (13)	
60–74	982 (18)	2035 (22)	223 (21)		161 (12)	213 (17)	68 (18)	
75–89	1609 (29)	3147 (34)	253 (24)		293 (21)	390 (32)	90 (24)	
90–104	1287 (23)	2164 (24)	83 (8)		344 (25)	343 (28)	57 (15)	
105–119	453 (8)	259 (3)	16 (2)		171 (12)	92 (7)	23 (6)	
≥ 120	205 (4)	24 (0)	3 (0)		115 (8)	23 (2)	5 (1)	
Diabetes mellitus	573 (10)	863 (9)	186 (18)	< 0.01	265 (19)	193 (16)	105 (27)	< 0.01
Hypertension	2337 (42)	4174 (46)	664 (63)	< 0.01	553 (40)	500 (40)	192 (50)	< 0.01
CVD	1184 (22)	2175 (24)	529 (50)	< 0.01	327 (23)	404 (33)	205 (54)	< 0.01
Heart failure	498 (9)	927 (10)	405 (38)	< 0.01	166 (12)	188 (15)	143 (37)	< 0.01
RA	466 (8)	847 (9)	89 (8)	0.23	126 (9)	131 (11)	14 (4)	< 0.01
Fractures (lumbar, femur)*	524 (10)	1033 (11)	335 (32)	< 0.01	89 (6)	195 (16)	87 (23)	< 0.01
Fracture, any site	1951 (35)	4121 (45)	607 (57)	< 0.01	370 (27)	503 (41)	170 (45)	< 0.01
MM	30 (1)	30 (0)	12 (1)	< 0.01	15 (1)	12 (1)	7 (2)	0.37
Breast cancer	349 (6)	986 (11)	96 (9)	< 0.01	–	–	–	
Prostate cancer	–	–	–		77 (6)	141 (11)	63 (16)	< 0.01
Colon and rectum cancer	56 (1)	134 (1)	27 (3)	< 0.01	13 (1)	14 (1)	12 (3)	< 0.01
Corticosteroids	1592 (29)	2984 (33)	313 (30)	< 0.01	468 (34)	519 (42)	129 (34)	< 0.01
Vitamin D2/D3	2652 (48)	6378 (70)	515 (49)	< 0.01	393 (28)	742 (60)	124 (32)	< 0.01
SERMs	174 (3)	282 (3)	20 (2)	0.08	3 (0)	2 (0)	1 (0)	0.91
Calcium	2737 (50)	6491 (71)	546 (52)	< 0.01	510 (37)	767 (62)	152 (40)	< 0.01
Denosumab	19 (0)	8 (0)	1 (0)	< 0.01	1 (0)	0 (0)	1 (0)	0.22

Median, P25, and P75 for continuous variables and n/% for categorical ones. eGFR, as mL/min/1.73 m^2

*Lumbar spine and femoral fractures only

Table 4 Baseline characteristics according to the occurrence of BSP use or death in Geisinger

	Women				Men			
	No BSP $n = 6333$	BSP $n = 9947$	Death $n = 1045$	p value	No BSP $n = 1334$	BSP $n = 1702$	Death $n = 532$	p value
Age (years)	68 (59, 77)	71 (63, 79)	81 (71, 88)	< 0.001	66 (54, 75)	74 (64, 81)	78 (67, 84)	< 0.001
Race (white)	6196 (98%)	9787 (98%)	1035 (99%)	< 0.001	1298 (97%)	1687 (99%)	527 (99%)	0.002
BMI (kg/m^2)	29 (25, 34)	27 (24, 32)	26 (22, 31)	< 0.001	29 (25, 33)	27 (24, 30)	27 (23, 30)	< 0.001
Smoking				0.02				< 0.001
Never smoker	3494 (58%)	5667 (59%)	539 (56%)		401 (32%)	505 (31%)	124 (25%)	
Former smoker	1767 (29%)	2691 (28%)	316 (33%)		628 (49%)	904 (55%)	296 (58%)	
Current smoker	797 (13%)	1307 (14%)	115 (12%)		241 (19%)	230 (14%)	86 (17%)	
eGFR				< 0.001				< 0.001
Dialysis	32 (1%)	12 (0%)	30 (3%)		16 (1%)	6 (0%)	20 (4%)	
≤ 29	111 (2%)	159 (2%)	121 (12%)		20 (1%)	11 (1%)	24 (5%)	
30–44	433 (7%)	721 (7%)	191 (18%)		65 (5%)	114 (7%)	71 (13%)	
45–59	924 (15%)	1699 (17%)	201 (19%)		164 (12%)	262 (15%)	102 (19%)	
60–74	1457 (23%)	2448 (25%)	179 (17%)		237 (18%)	397 (23%)	106 (20%)	
75–89	1675 (26%)	2663 (27%)	187 (18%)		341 (26%)	497 (29%)	102 (19%)	
90–104	1355 (21%)	1942 (20%)	100 (10%)		309 (23%)	313 (18%)	70 (13%)	
105–119	268 (4%)	256 (3%)	28 (3%)		126 (9%)	77 (5%)	27 (5%)	
≥ 120	78 (1%)	47 (0%)	8 (1%)		56 (4%)	25 (1%)	10 (2%)	
Diabetes mellitus	1380 (22%)	2000 (20%)	369 (35%)	< 0.001	326 (24%)	419 (25%)	189 (36%)	< 0.001
Hypertension	3975 (63%)	6090 (61%)	809 (77%)	< 0.001	831 (62%)	1067 (63%)	403 (76%)	< 0.001
CVD	1735 (27%)	2769 (28%)	572 (55%)	< 0.001	526 (39%)	818 (48%)	340 (64%)	< 0.001
Heart failure	391 (6%)	702 (7%)	280 (27%)	< 0.001	123 (9%)	223 (13%)	168 (32%)	< 0.001
Rheumatoid arthritis	231 (4%)	577 (6%)	46 (4%)	< 0.001	54 (4%)	184 (11%)	16 (3%)	< 0.001
Fractures (lumbar, femur)*	221 (3%)	346 (3%)	135 (13%)	< 0.001	122 (9%)	178 (10%)	83 (16%)	< 0.001
Fracture, any site	741 (12%)	1188 (12%)	253 (24%)	< 0.001	304 (23%)	344 (20%)	141 (27%)	0.007
Multiple myeloma	12 (0%)	14 (0%)	16 (2%)	< 0.001	18 (1%)	7 (0%)	18 (3%)	< 0.001
Breast cancer	465 (7%)	635 (6%)	92 (9%)	0.003	–	–	–	
Prostate cancer	–	–	–		118 (9%)	207 (12%)	75 (14%)	0.001
Colon and rectum cancer	79 (1%)	141 (1%)	33 (3%)	< 0.001	25 (2%)	33 (2%)	19 (4%)	0.05
Corticosteroids	2439 (39%)	4023 (40%)	399 (38%)	0.03	653 (49%)	1048 (62%)	270 (51%)	< 0.001
HRT	1512 (24%)	2338 (24%)	137 (13%)	< 0.001	–	–	–	
SERMs	307 (5%)	359 (4%)	58 (6%)	< 0.001	–	–	–	
Calcium	2936 (46%)	5301 (53%)	408 (39%)	< 0.001	312 (23%)	737 (43%)	117 (22%)	< 0.001
Vitamin D2/D3	3360 (53%)	5860 (59%)	527 (50%)	< 0.001	524 (39%)	984 (58%)	204 (38%)	< 0.001
Denosumab	41 (1%)	8 (0%)	9 (1%)	< 0.001	2 (0%)	0 (0%)	5 (1%)	< 0.001

Median, P25, and P75 for continuous variables and n/% for categorical ones. eGFR, as mL/min/1.73 m^2

*Lumbar spine and femoral fractures only

not as high as expected, considering that these are recommended maintenance drugs that should be co-administered with other osteoporosis treatments. These findings are consistent with prior literature. A study of older women from Gothenburg, Sweden, showed that only 22% of those eligible for anti-reabsortive treatment were treated and similar findings have been reported in other European countries [23–25]. Previous studies on populations seen in specialized clinics in Geisinger showed a higher rate of treatment in comparison to our results, but these differences may be related to different practices between specialized versus primary care [26, 27].

In our analysis, factors associated with lower odds of prescription of BSP in the two studies were eGFR category, age, hypertension, and baseline drugs. In addition, in SCREAM, history of fracture at any site and breast cancer were positively associated with BSP use, whereas in Geisinger, race, BMI, current smoking, and rheumatoid arthritis were related to BSP prescription. However, we note that our data was

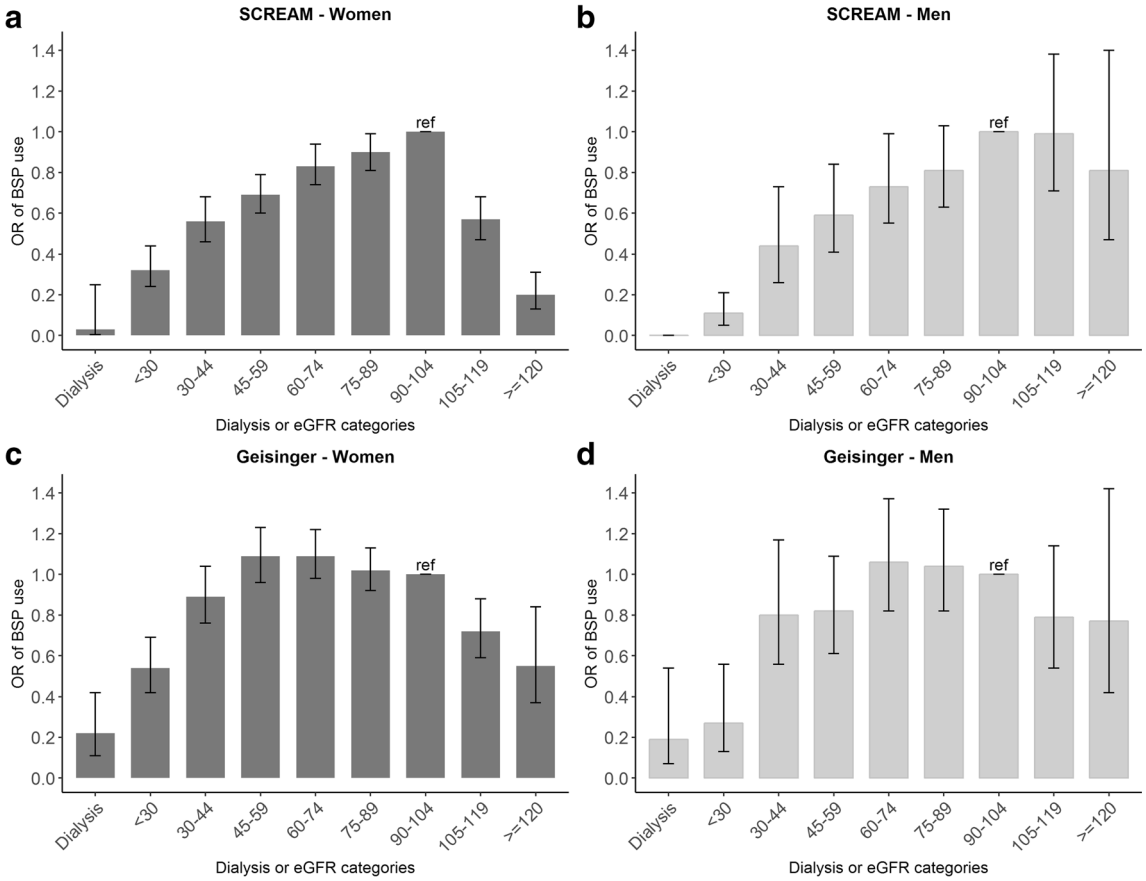

Fig. 1 Adjusted OR of BSP use among osteoporosis patients in SCREAM and Geisinger by eGFR categories. Footnote: Bars represent adjusted odds ratio of BSP use (using no use of BSP as the reference group) from multinomial logistic regression model after adjustment for age, comorbidities, and drugs at baseline in SCREAM (A and B) and same plus race, BMI, and smoking in Geisinger (C and D). Whiskers represent 95%CI of the estimate. Reference group was eGFR category 90–104 mL/min/1.73 m^2. OR, odds ratio; eGFR, estimated glomerular filtration ratio

extracted from administrative records, and we lacked information on some key variables related to osteoporosis treatment, such as DEXA, alcoholism, and family history of fractures, likely to drive the clinical decision about treatment. The decline in use that we observed in Geisinger over time is also consistent with other studies that have reported a trend to decreased use of BSP for the treatment of osteoporosis in the USA [18]. In this study, the authors suggest that the decline reported may be related to the release by the FDA of a drug safety communication in 2010 warning about increased risk of atypical fractures with BSP, particularly with prolonged use [17, 18]. In our study, however, we could not ascertain reasons for the observed difference in BSP prescription rate between 2006 and 2011 and 2012 and2016.

Treatment of osteoporosis in the CKD population is complex. First, bone disease in patients with CKD may reflect not only osteoporosis but also other CKD-related bone manifestations, such as high turnover disease, low turnover disease and osteomalacia [28–30]. The diagnosis of these conditions impacts treatment. For example, BSPs can be harmful in low turnover disease and osteomalacia by aggravating the already decreased bone formation rate. However, since no serum or urinary biomarker has an accurate performance, a bone biopsy is still required to distinguish among these conditions, although not widely performed [16, 31]. Second, there are few studies evaluating the efficacy of BSPs in the CKD population. The recommendations for BSP use are based on post hoc analysis of large randomized clinical trials restricted to those individuals with moderate reductions of eGFR [32, 33]. The KDIGO guidelines attempted to balance these issues and recommended BPS in patients with no or moderate declines in GFR and without biochemical evidence of CKD-MBD and who are at increased risk for fractures [16].

In SCREAM, the lower use of BSP in participants with eGFR from 30 to 89 mL/min/1.73 m^2 might reflect ongoing concerns with use of BSP in patients with CKD regardless of the guidelines, or that these people were not at high risk for fractures and clinicians are appropriately deciding to hold off therapy. SCREAM presented a higher rate of history of fractures in comparison to Geisinger. Previous studies have shown higher age-standardized fracture incidence in Sweden in comparison to the USA, but in our study, we could not evaluate if

Table 5 Adjusted odds ratio of BSP use for the covariates in the fully adjusted model in SCREAM and in Geisinger

	SCREAM		Geisinger	
	Women	Men	Women	Men
Time period (2012–2016 vs. 2006–2011)	–	–	0.56 (0.52, 0.60)	0.67 (0.57, 0.78)
Age, per 10 years	1.29 (1.25, 1.33)	1.44 (1.36, 1.53)	1.18 (1.13, 1.22)	1.27 (1.17, 1.38)
Race	–	–		
White	–	–	ref	ref
Black	–	–	0.56 (0.39, 0.80)	0.31 (0.12, 0.79)
Asian	–	–	1.07 (0.69, 1.66)	0.86 (0.19, 3.87)
Other	–	–	1.98 (1.06, 3.70)	0.65 (0.10, 4.34)
BMI, per 5 kg/m^2	–	–	0.90 (0.88, 0.93)	0.84 (0.78, 0.90)
Smoking	–	–		
Never smoker	–	–	Ref	Ref
Former smoker	–	–	0.98 (0.91, 1.06)	0.90 (0.75, 1.07)
Current smoker	–	–	1.13 (1.02, 1.26)	0.76 (0.60, 0.97)
eGFR ml/min/1.73 m^2	*	*	*	*
Diabetes mellitus	0.92 (0.82, 1.04)	0.86 (0.68, 1.08)	0.96 (0.88, 1.04)	1.02 (0.85, 1.22)
Hypertension	0.89 (0.82, 0.96)	0.86 (0.71, 1.05)	0.87 (0.80, 0.94)	0.81 (0.68, 0.97)
CVD	0.91 (0.84, 1.00)	1.09 (0.88, 1.34)	0.85 (0.79, 0.92)	1.01 (0.85, 1.19)
Heart failure	0.92 (0.81, 1.04)	1.04 (0.79, 1.35)	0.94 (0.82, 1.07)	0.83 (0.66, 1.04)
RA	1.01 (0.88, 1.14)	0.79 (0.59, 1.06)	1.56 (1.32, 1.84)	2.05 (1.49, 2.84)
Fractures (lumbar, femur)[#]	0.80 (0.70, 0.91)	1.39 (1.00, 1.92)	0.78 (0.63, 0.96)	1.15 (0.84, 1.59)
Fracture, any site	1.40 (1.29, 1.52)	1.49 (1.21, 1.83)	1.12 (0.99, 1.26)	0.88 (0.69, 1.11)
MM	0.74 (0.43, 1.27)	1.00 (0.43, 2.31)	0.55 (0.28, 1.09)	0.17 (0.07, 0.42)
Breast cancer	1.80 (1.56, 2.06)	–	0.89 (0.78, 1.02)	–
Prostate cancer	–	1.13 (0.82, 1.55)	–	0.96 (0.75, 1.22)
Colon and rectum cancer	1.14 (0.82, 1.57)	0.64 (0.29, 1.45)	0.88 (0.68, 1.16)	0.76 (0.46, 1.24)
Corticosteroids	1.14 (1.05, 1.24)	1.09 (0.90, 1.32)	1.06 (0.99, 1.14)	1.48 (1.26, 1.73)
HRT	–	–	0.96 (0.89, 1.03)	–
SERMs	0.61 (0.50, 0.75)	0.58 (0.07, 5.21)	0.70 (0.59, 0.83)	–
Calcium	2.00 (1.49, 2.68)	1.98 (1.13, 3.49)	1.15 (1.05, 1.25)	1.80 (1.48, 2.20)
Vitamin D	1.11 (0.83, 1.49)	1.56 (0.89, 2.75)	1.16 (1.06, 1.28)	1.44 (1.20, 1.74)
Denosumab	0.18 (0.08, 0.43)	0.00 (0.00, 0.00)	0.13 (0.06, 0.28)	–

RA, rheumatoid arthritis; *MM*, multiple myeloma; *HRT*, hormone replacement therapy; *SERMs*, selective estrogen receptor modulators

*shown in Table 3 and Fig. 1. We present here odds ratios for the covariates used in the fully adjusted multinomial logistic regression model of eGFR categories on BSP use and death (using "no BSP use" as the reference group)

[#] Lumbar spine and femoral fractures only

the difference observed was simply related to different coding practices between the two healthcare systems [34, 35]. We did not have PTH levels and therefore could not identify participants in whom it was appropriate to hold BSP, nor did we have sufficient information to compute risk of fractures. However, a prior study shows that elevated PTH is not common in these eGFR categories [36].

KDIGO recommends that BSP should not generally be used for eGFR < 30 mL/min/1.73 m^2. It is therefore appropriate that we observe lower use in this eGFR category in both studies. Conversely, a sizeable proportion of participants still had prescriptions even at this eGFR category. This might indicate that clinicians are not attuned to the recommendations by KDIGO and might represent a potential for quality improvement.

In both Geisinger and SCREAM, women, but not men, with eGFR > 104 mL/min/1.73 m^2 had a lower rate of BSP use, even after adjustments. These women were younger and also presented an increased risk of death in comparison to the reference group, suggesting that the decreased use of BSP may be related to conditions of illnesses that were not identified in this analysis. eGFRcr at this level might be more reflective of low muscle mass rather than high GFR. As such, higher eGFR

values may be related to reduced muscle mass secondary to chronic illness, increasing therefore the likelihood of misclassification bias by eGFR in these people. It is interesting that we did not find this association in men. Men have higher serum creatinine values than women and this might indicate that clinicians are not using eGFR values to dose medications.

Our study strengths were a large sample of people with incident osteoporosis, the use of two health systems from different countries, and the adjustment for the competing risk of death in both, an issue especially relevant given the high mortality rate of CKD. Our study presents also several limitations. First, data is derived from EHR data and we did not perform internal validation for the osteoporosis coding, a fact that can lead to some degree of ascertainment bias and misclassification. This also limited our ability to understand factors associated with BSP prescription. Second, although we did compute use at baseline, we did not compute the incidence of other first-line treatments for osteoporosis, which may occur *in lieu* of BSP. However, denosumab, teriparatide, raloxifene, and HRT are either more expensive drugs not commonly prescribed or are considered by many as second-line therapy in comparison to BSPs. Third, there may be some underestimation in the usage of BSP: in Geisinger, we could not account for BSP prescribed from other providers, and in SCREAM, intravenous BSPs administered during hospitalizations may not appear as dispensation. In addition, calcium and vitamin D ascertainment may be limited by partial assessment of over-the-counter use, particularly in Geisinger. Fourth, we did not have data on PTH, vitamin D, and DEXA, nor could compute the risk of fractures using validated scores such as FRAX and others [37, 38]. We also could not ascertain CKD and albuminuria as recommended by guidelines and used eGFR alone instead. Lastly, we limited our analysis to 3 years of follow-up so our results do not take into account BSP being prescribed after this period.

In conclusion, our study shows that approximately half of the people diagnosed with osteoporosis received BSP treatment in two large health systems. Practices of BSP prescription in relation to eGFR varied between the two studies, but persons with lower eGFR were less likely to receive BSP treatment. While it is true that BSP use in CKD should be considered carefully, undertreatment of osteoporosis increases the risk for fractures and their associated risk for morbidity and mortality. Studies focusing on specific concerns regarding BSP use in osteoporosis, such as duration of treatment, head-to-head comparison to other first-line treatment options, and efficacy and safety in the CKD population are needed.

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Compliance with ethical standards

Conflict of interest Dr. Evans reports funding to Karolinska Institutet from Astra Zeneca and Astellas outside this work and payment for lectures (Astellas, Vifor Pharma) and advisory board (Astra Zeneca, Astellas). Dr. Grams reports funding from the National Kidney Foundation and the NIH. Dr. Inker reports funding to Tufts Medical Center for research and contracts with the NIH, NKF, Dialysis Inc., Retrophin, Omeros, and Reata Pharmaceuticals. She has consulting agreements with Tricida. Dr. Carrero reports funding to Karolinska Institutet for research from AstraZeneca, Viforpharma, Astellas, and MSD outside the submitted work. He has performed consultation for Fresenius and Baxter. All the other authors declare that they have no conflict of interest

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