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Article

Real-World Use of Bone-Modifying Agents in Metastatic Castration-Sensitive Prostate Cancer

Aaron P. Mitchell, MD, MPH, [1,2,*] Akriti Mishra Meza, MS, [1] Katherine S. Panageas, DrPH,[1] Allison Lipitz-Snyderman, PhD,[1] Peter B. Bach, MD, MAPP, [1] Michael J. Morris, MD [2]

[1]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; and [2]Department of Medicine, Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[*]**Correspondence to:** Aaron Mitchell, MD, MPH, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 485 Lexington Ave, 2nd Floor, New York, NY 10017, USA (e-mail: mitchea2@mskcc.org).

Abstract

Background: Bone-modifying agent (BMA) therapy is recommended for metastatic castration-resistant prostate cancer but not metastatic castration-sensitive prostate cancer (mCSPC). BMA treatment in mCSPC may therefore constitute overuse. **Methods:** In this retrospective cohort study using linked Surveillance, Epidemiology, and End Results–Medicare data, we included patients diagnosed with stage IV prostate adenocarcinoma from 2007 to 2015 who were 66 years of age or older at diagnosis and had received androgen-deprivation or antiandrogen therapy. We excluded patients who had previously received BMAs or had existing osteoporosis, osteopenia, hypercalcemia, or prior bone fracture. The primary outcome was receipt of BMA (zoledronic acid or denosumab) within 180 days of diagnosis (emergence of CRPC within this time frame is unlikely). The secondary outcome was receipt of a BMA within 90 days. Exposures of interest included practice location (physician office vs hospital outpatient) and the specialty (medical oncologist vs urologist) of the treating physician. **Results:** Our sample included 2627 patients, of whom 52.9% were treated by medical oncologists and 47.1% by urologists; 77.7% and 22.3% received care in physician office and hospital outpatient locations, respectively. Overall, 23.6% received a BMA within 180 days; 18.4% did within 90 days. BMA therapy was more common among patients treated by oncologists (odds ratio = 8.23, 95% confidence interval = 6.41 to 10.57) and in physician office locations (odds ratio = 1.33, 95% confidence interval = 1.06 to 1.69). Utilization has increased: 17.3% of patients received BMAs from 2007 to 2009 (17.3% zoledronic acid, 0% denosumab) and 28.1% from 2012 to 2015 (8.4% zoledronic acid, 20.3% denosumab). **Conclusions:** Among patients with mCSPC who had no evidence of high osteoporotic fracture risk, more than one-quarter have received BMAs in recent years. This overuse may lead to excess costs and toxicity.

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Prostate cancer (PCa) is the most prevalent cancer among US men, causing more than 33 000 deaths annually (1). A leading cause of morbidity among patients with advanced PCa is skeletal-related events (SREs), which include pathologic fracture, severe bone pain that requires intervention, hypercalcemia, and spinal cord compression. Of men with PCa and bone metastasis, 30% to 50% will experience 1 or more SREs (2,3). SREs cause clinically significant loss of function and quality of life (4), and they are associated with increased mortality (4,5).

Bone-modifying agents (BMAs), including bisphosphonates and denosumab, are recommended for SRE prevention among patients with metastatic, castration-resistant PCa (mCRPC) with bone involvement (6). Bisphosphonate zoledronic acid and the RANKL inhibitor denosumab are effective in SRE prevention in PCa (7–9). Distinct from SRE prevention, BMAs are also recommended for men at high risk of osteoporotic fracture (6,10), which is especially relevant to patients with PCa because long-term androgen-deprivation therapy accelerates bone mineral density loss.

In contrast to mCRPC, there is evidence against the use of BMAs in metastatic, castration-sensitive prostate cancer (mCSPC). Two phase III randomized trials found no benefit in SRE reduction with the early initiation of zoledronic acid in the mCSPC setting (11,12). Denosumab has demonstrated efficacy only among patients with mCRPC (9) and has not been studied in mCSPC. BMAs can cause severe toxicities. Painful acute-phase reactions are common, and renal injury, hypocalcemia, and osteonecrosis of the jaw are well documented (13–17).

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BMAs are expensive to the health care system (18,19), as well—especially denosumab; a year of denosumab costs Medicare more than $27 000, compared with $212 for zoledronic acid (20). Given the absence of benefit and the potential for toxicity and excess costs, BMAs are not recommended for patients with PCa who do not have either mCRPC or high fracture risk (6,21).

The real-world use of BMAs among patients with mCSPC has not been previously described. Factors that may have affected BMA use in recent years include the approval of denosumab in 2010; the emergence of clinical data in 2013 that zoledronic acid does not prevent SREs in mCSPC (11,22); and financial incentives under "buy and bill," in which reimbursement is proportional to drug price (23). These financial incentives favor BMA administration, especially denosumab: denosumab costs approximately $1700 per dose at market entry vs approximately $900 per dose for zoledronic acid (24), a difference that became much greater after the entry of generic zoledronic acid in 2014 (20).

We aimed to characterize BMA use among patients with mCSPC who had no evidence of increased fracture risk, which may represent overuse. We sought to understand temporal trends in the specific drugs used and associated provider factors. Factors of interest included physician specialty and treatment billing location. We hypothesized that medical oncologists' specialized training would result in greater guideline-concordant BMA use: higher BMA use among patients with increased osteoporotic fracture risk and lower use among patients with mCSPC without that indication. We hypothesized greater use in physician office settings, which has been associated with greater responsiveness to reimbursement incentives (25,26).

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Methods

Patient Population

We used linked Surveillance, Epidemiology, and End Results (SEER)–Medicare data. We included fee-for-service Medicare beneficiaries diagnosed with stage IV prostate adenocarcinoma from 2007 to 2015. Patients were eligible if PCa was their first cancer diagnosis or their second cancer diagnosis if their first had occurred 3 years or more prior. Patients were 66 years of age or older at diagnosis and not diagnosed at death. We required continuous enrollment in Medicare Parts A and B and not Medicare Advantage for at least 240 days before the month of diagnosis and 180 days after diagnosis. We required continuous enrollment in Medicare Part D from the month of diagnosis to 180 days after. We included patients with a first claim for a hormone therapy (HT) agent (androgen-deprivation therapy or an antiandrogen) occurring within 60 days before the month of diagnosis (allowing for the possibility that some patients may begin treatment when PCa is suspected but not yet confirmed) to 180 days after. We also excluded patients receiving bisphosphonate therapy before PCa diagnosis or who had a prior diagnosis of hypercalcemia, osteoporosis, osteopenia, or bone fracture (Supplementary Table 1,Supplementary Figure 1, available online).

In addition to the primary cohort described above, we evaluated BMA use among 2 other mCSPC cohorts. The first consisted of patients who had a prior diagnosis of osteoporosis, osteopenia, hypercalcemia, or bone fracture (elevated fracture risk [EFR] cohort) to assess BMA use among those who may have had an appropriate BMA indication. The second consisted of a subset of the primary cohort that met the additional requirement of having no claims for osteoporosis, osteopenia, any SRE-defining event, or dual-energy x-ray absorptiometry (DEXA) during the follow-up period (lowest fracture risk [LFR] cohort) to address the possibility that some patients might be appropriately diagnosed and treated for high osteoporotic fracture risk after PCa diagnosis has occurred (Supplementary Figure 1, available online).

To assess the intended use (SRE prevention or osteoporotic fracture prevention) of BMA administration, we measured denosumab dosing among patients who received that drug (120 mg per month is administered for SRE prevention vs 60 mg every 6 months for osteoporosis).

The Memorial Sloan Kettering Institutional Review Board found this research exempt under 45 CFR 46.104(d) (4).

Outcome Definition

The primary outcome was any claim for a BMA (zoledronic acid or denosumab) within 180 days of diagnosis. This time point was selected because the emergence, diagnosis, and treatment of mCRPC is unlikely to occur in fewer than 180 days, and patients can therefore be assumed to have mCSPC within this interval. Because a small number of patients may develop mCRPC in less than 180 days, we also assessed receipt of BMAs within 90 days as a secondary outcome. In the EFR cohort specifically, we also included other bisphosphonates (eg, alendronate) in the outcome because these drugs are appropriate for osteoporotic fracture prevention.

Patient Characteristics and Potential Confounders

We identified patient characteristics that may be associated with receipt of BMA therapy. These included age, calendar year of diagnosis, race and ethnicity, history of kidney disease, modified Charlson Comorbidity Index (27), frailty (28), and zip code–level median income (American Community Survey, 2008-2012).

We identified the treatment billing location (hospital outpatient vs physician office), defined by the location of the following: 1) the first billed claim for an HT agent (patients treated with a physician-administered drug) or 2) the first billed BMA claim (patients where BMA claims preceded any HT claims) or 3) the evaluation and management claim of the patient's first postdiagnosis encounter with a physician specialty type of urology or medical oncology (patients for whom HT was a prescription drug) (25,29,30). The specialty of the treating physician was identified using evaluation and management claims and categorized as either "Urologist only" ($\geq$1 visit with a urologist and none with a medical oncologist during the outcome period) vs "Oncologist involved" ($\geq$1 visit with a medical oncologist during the outcome period).

Statistical Analysis

We calculated descriptive statistics for patient characteristics and outcomes of interest. To assess characteristics associated with BMA use, we performed multivariable logistic regression using the full cohorts. To assess factors associated with the use of denosumab specifically, we performed logistic regression on the subset of each cohort that received BMA therapy (either drug) and was diagnosed during the time period that both drugs were available (2010 onwards).

Estimates with 95% confidence intervals (CIs), excluding the null, were considered statistically significant. All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC).

Results

The primary cohort comprised 2627 men diagnosed with stage IV PCa from 2007 to 2015 (Supplementary Figure 1, available online). Of these, 1390 (52.9%) had medical oncologists involved in their care, while 1237 (47.1%) saw only urologists (Supplementary Table 2, available online); 586 were treated in a hospital outpatient location and the remaining 2041 in a physician office location. Median age at diagnosis was 75 years, and 77.0% of patients were White. The EFR cohort comprised 1586 patients, and the LFR cohort comprised 2415 patients (Table 1).

Across the entire study period, 23.6% of patients received BMAs within 180 days of diagnosis, relatively evenly split between denosumab and zoledronic acid (Table 2). Receipt of BMAs was higher in the EFR cohort (41%) and lower in the LFR cohort (17%). The proportion of patients who received BMAs within 90 days was slightly lower at 18.4% (Table 3).

BMA use increased during the study period. Within the primary cohort, the proportion of patients receiving BMAs within 180 days was 17.3% during 2007-2009 and 28.1% during 2012-2015. The use of BMAs increased within the EFR and LFR cohorts, as well (Figure 1).

On multivariable regression, the only factors statistically associated with receipt of BMAs were calendar year of diagnosis (2012 or later vs before 2010; odds ratio [OR] = 1.67, 95% CI = 1.31 to 2.13), treatment billing location (physician office vs hospital outpatient; OR = 1.33, 95% CI = 1.06 to 1.69), and physician specialty (oncologist involved vs urologist only; OR = 8.23, 95% CI = 6.41 to 10.57) (Table 4).

The relative use of the 2 BMA drugs shifted substantially across the study period. Following its approval in 2010, denosumab quickly increased to constitute a majority of BMAs by 2012, while zoledronic acid use declined (Figure 2). Denosumab use has increased from 0% in 2007-2009 to 20.3% of patients during 2012-2015, while zoledronic acid declined from 17.3% to 8.4% of patients.

Among the subset of patients who received BMAs, factors associated with receipt of denosumab were treatment within the physician office setting (vs hospital outpatient; OR = 2.68, 95% CI = 1.63 to 4.41), age 80 years or older (vs <80 years; OR = 3.09, 95% CI = 1.71 to 5.57), and treatment by urologist only (vs oncologist involved; OR = 2.81, 95% CI = 1.33 to 5.93) (Supplementary Table 3, available online). Within the primary cohort, 282 of 306 patients who received denosumab (92.2%) received the SRE-prevention dose of 120 mg (not shown).

Discussion

For metastatic PCa, National Comprehensive Cancer Network (NCCN) guidelines recommend BMA therapy for either castration-resistant disease or prevention of osteoporotic fractures in high-risk patients (6). Among patients with mCSPC and without a high risk of osteoporotic fracture, BMA therapy may constitute overuse. We found that 24% of patients in this population received BMA therapy. To our knowledge, this is the first study of BMA use patterns in mCSPC. Although a minority, this is a substantial portion of patients and, because PCa is common, reflects a large number of individuals who may be exposed to unnecessary treatment as well as the associated toxicity and financial cost.

These findings have direct implications for patient outcomes. High-quality clinical trials have found that patients with mCSPC do not benefit from BMA therapy (11,12). As the toxicities of BMAs are well established, it is possible that patients with mCSPC experience net harm from BMA therapy. BMA therapy may also result in avoidable financial consequences. Patients and caregivers may incur additional expenses for transportation and missed work for treatment (31,32), especially for denosumab, which is administered monthly (zoledronic acid can be administered every 3 months). The out-of-pocket cost for denosumab is substantial for Medicare beneficiaries who do not have supplemental insurance and can result in patients needing to seek financial assistance (33).

Our findings also have implications for health care system costs. Medicare reimbursement for zoledronic acid is $53 per infusion vs $2321 per denosumab injection (20). Given this price difference, denosumab is not cost-effective compared with zoledronic acid (19). Unnecessary costs therefore result from both BMA overuse and substitution of denosumab for zoledronic acid when BMA therapy is recommended. The observed increasing utilization of denosumab suggests avoidable spending without commensurate improvement in outcomes. Because PCa is common, the excess financial cost of BMA therapy to the health care system is likely to be substantial; further work is needed to estimate the magnitude of excess costs.

Disease characteristics were important determinants of BMA use. Patients with evidence of high osteoporotic fracture risk (EFR cohort) were more likely to receive BMAs. As BMA therapy would be guideline concordant within this population, higher utilization is appropriate. Although not all patients in the EFR cohort would have needed BMA therapy (eg, those with osteopenia and low Fracture Risk Assessment Tool [FRAX] score), our results suggest that BMAs may be underused for osteoporotic fracture prevention.

We did not find evidence that patient characteristics were associated with BMA use. The lack of association with renal disease is notable; zoledronic acid is more nephrotoxic than denosumab, providing a rationale to use denosumab over zoledronic acid among patients with this comorbidity. The absence of association suggests that a goal of minimizing nephrotoxicity is not an important factor in the increasing use of denosumab. These findings are consistent with observations from multiple myeloma, wherein denosumab use has increased even among patients for whom nephrotoxicity is not a concern (34).

In contrast, provider factors were important determinants of BMA use. Involvement of a medical oncologist was strongly associated with BMA use across all cohorts, which suggests differences among physician specialties with respect to their views of their own therapeutic role, with medical oncologists being more likely to initiate medical therapies such as BMAs. Potential provider-facing interventions aimed at better aligning BMA use with clinical practice guidelines may be more successful if focusing more on medical oncologists than other specialties.

Receiving treatment in the physician office location was associated with receipt of BMA therapy—specifically, denosumab. Higher denosumab use in the physician office could be related to ease of administration, lower availability of infusion chairs, or adherence to clinical pathways that promote its use. It could also reflect greater responsiveness to financial incentives, as the physician office setting has been associated with the delivery of other low-value but highly reimbursed cancer care services (25,26).

BMA therapy among patients with mCSPC increased during the study period. This increase was temporally correlated with the approval of denosumab in 2010. The dissemination of denosumab into clinical practice may therefore be a contributing factor to the overall increase, offsetting a concurrent decline in zoledronic acid use (Figure 2). Evidence that BMAs do not

Table 1. Patient characteristics[a]

Characteristic	Primary cohort (n = 2627)	EFR cohort (n = 1586)	LFR cohort (n = 2415)
Age at diagnosis, y			
Median (IQR)	75 (71-81)	78 (73-84)	75 (71-81)
Mean (SD)	76 (7)	79 (7)	76 (7)
Race, No. (%)			
Black	314 (12.0)	142 (9.0)	297 (12.3)
White	2022 (77.0)	1291 (81.4)	1851 (76.7)
Other	291 (11.1)	153 (9.7)	267 (11.1)
Year of diagnosis, No. (%)			
Before 2010	756 (28.8)	315 (19.9)	714 (29.6)
2010 or 2011	495 (18.8)	263 (16.6)	455 (18.8)
2012 or later	1376 (52.4)	1008 (63.6)	1246 (51.6)
No. of comorbid conditions, No. (%)			
0	1739 (66.2)	810 (51.1)	1597 (66.1)
1	471 (17.9)	332 (20.9)	431 (17.9)
≥2	417 (15.9)	444 (28.0)	387 (16.0)
Predicted probability of dependence in ADL[b], %			
Median (IQR)	6.6 (4.2-12.1)	10.2 (5.4-23.9)	6.6 (4.1-12.2)
Mean (SD)	11.5 (14.2)	19.5 (22.4)	11.5 (14.3)
Survival time, mo			
Median (IQR)	20 (11-35)	18 (10-29)	21 (11-36)
Mean (SD)	26 (20)	22 (17)	27 (21)
History of renal disease, No. (%)			
No	2142 (81.5)	1207 (76.1)	1969 (81.5)
Yes	485 (18.5)	379 (23.9)	446 (18.5)
Zip code median income, No. (%)			
<$50 000	1018 (39.7)	575 (37.2)	945 (40.1)
$50 000-$54 999	245 (9.6)	151 (9.8)	223 (9.5)
$55 000-$59 999	200 (7.8)	130 (8.4)	180 (7.6)
$60 000-$69 999	333 (13.0)	208 (13.5)	309 (13.1)
$70 000 or more	768 (30.0)	480 (31.1)	698 (29.6)
Unknown	63	42	60

[a]The EFR cohort comprised patients with a diagnosis of osteoporosis, osteopenia, or bone fracture before PCa diagnosis. The LFR cohort comprised the subset of the primary cohort that had no claims for osteoporosis, osteopenia, any SRE-defining event, or DEXA during the outcome period. ADL = activity of daily living; DEXA = dual-energy x-ray absorptiometry; EFR = elevated fracture risk; IQR = interquartile range; LFR = lowest fracture risk; PCa = prostate cancer; SD = standard deviation; SRE = skeletal-related event.
[b]Faurot algorithm (28).

Table 2. Primary outcome[a]

Characteristic	Primary cohort, No. (%)	EFR cohort, No. (%)	LFR cohort, No. (%)
Total No.	2627	1586	2415
Any BMA	619 (23.6)	643[b] (40.5)	407 (16.9)
Denosumab	306 (11.7)	296 (18.7)	212 (8.8)
Zoledronic acid	325 (12.4)	271 (171)	203 (8.4)

[a]Receipt of BMAs within 180 days of diagnosis. Because some patients received both denosumab and zoledronic acid, the "Any BMA" total may be less than the sum of the 2 individual drugs. The EFR cohort comprised patients with a diagnosis of osteoporosis, osteopenia, or bone fracture before PCa diagnosis. The LFR cohort comprised the subset of the primary cohort that had no claims for osteoporosis, osteopenia, any SRE, or DEXA during the outcome period. BMA = bone modifying agent; DEXA = dual-energy x-ray absorptiometry; EFR = elevated fracture risk; LFR = lowest fracture risk; PCa = prostate cancer; SRE = skeletal-related event.
[b]For the EFR cohort, "Any BMA" also includes 88 patients who received oral bisphosphonates because orally administered bisphosphonates are appropriate for osteoporotic fracture prevention, and this cohort contains patients with evidence of high osteoporotic fracture risk.

Table 3. Receipt of bone-modifying agents within 90 days of diagnosis

Characteristic	Primary cohort, No. (%)	EFR cohort, No. (%)	LFR cohort, No. (%)
Total No.	2627	1586	2415
Any BMA	483 (18.4)	538[a] (33.9)	336 (13.9)
Denosumab	242 (9.2)	232 (14.6)	171 (7.1)
Zoledronic acid	246 (9.4)	225 (14.2)	167 (6.9)

[a]For the EFR cohort, "Any BMA" also includes 88 patients who received oral bisphosphonates because orally administered bisphosphonates are appropriate for osteoporotic fracture prevention, and this cohort contains patients with evidence of high osteoporotic fracture risk. BMA = bone-modifying agent; EFR = elevated fracture risk; LFR = lowest fracture risk.

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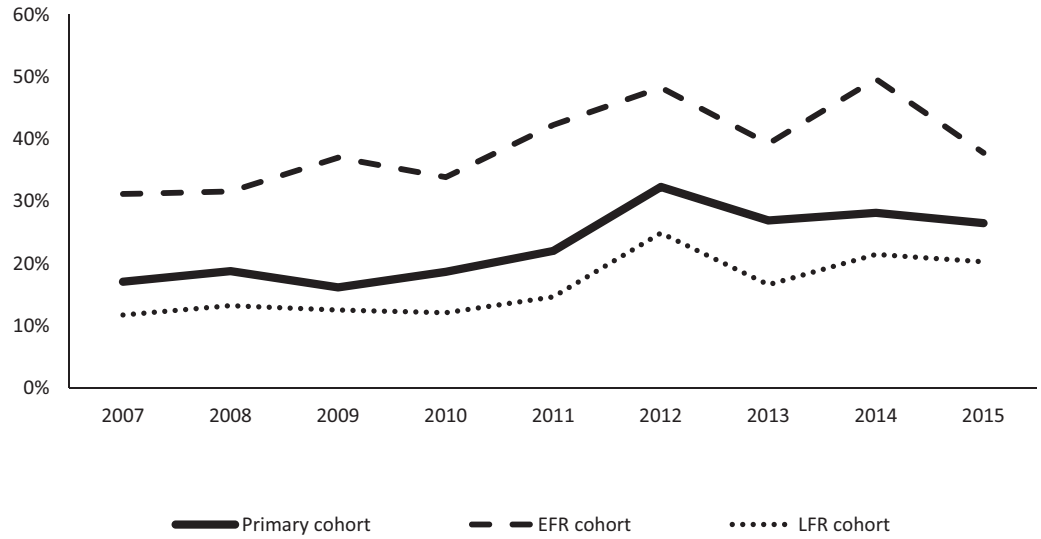

Figure 1. Proportion of patients who received any bone-modifying agent within 180 days of diagnosis over time. The elevated fracture risk (EFR) cohort (n = 1586) comprised patients with a diagnosis of osteoporosis, osteopenia, or bone fracture before prostate cancer diagnosis. The lowest fracture risk (LFR) cohort (n = 2415) comprised the subset of the primary cohort that had no claims for osteoporosis, osteopenia, any skeletal-related event, or dual-energy x-ray absorptiometry during the outcome period.

Table 4. Factors associated with receipt of any bone-modifying agent within 180 days of diagnosis[a]

Effect	Primary cohort OR (95% CI)	EFR cohort OR (95% CI)	LFR cohort OR (95% CI)
Location			
Hospital outpatient location	[Referent]	[Referent]	[Referent]
Physician office location	1.33 (1.06 to 1.69)	1.34 (1.04 to 1.73)	1.21 (0.93 to 1.58)
Year of diagnosis			
Before 2010	[Referent]	[Referent]	[Referent]
2010-2011	1.24 (0.91 to 1.70)	1.10 (0.75 to 1.59)	1.12 (0.77 to 1.63)
2012 or later	1.67 (1.31 to 2.13)	1.23 (0.91 to 1.65)	1.64 (1.24 to 2.17)
Age, y			
<80	[Referent]	[Referent]	[Referent]
≥80	1.04 (0.81 to 1.32)	1.17 (0.92 to 1.48)	1.24 (0.95 to 1.63)
Race			
Black	0.90 (0.64 to 1.27)	0.71 (0.46 to 1.08)	0.98 (0.66 to 1.44)
White	[Referent]	[Referent]	[Referent]
Other	1.04 (0.75 to 1.44)	1.24 (0.85 to 1.80)	1.01 (0.70 to 1.48)
No. of comorbid conditions			
None	[Referent]	[Referent]	[Referent]
1	1.24 (0.95 to 1.60)	1.05 (0.79 to 1.39)	1.27 (0.94 to 1.71)
≥2	1.01 (0.75 to 1.38)	1.12 (0.83 to 1.52)	1.12 (0.79 to 1.58)
History of renal failure (vs no history of renal failure)	1.07 (0.81 to 1.40)	0.85 (0.64 to 1.13)	1.07 (0.78 to 1.46)
Physician specialty			
Urologist only	[Referent]	[Referent]	[Referent]
Oncologist involved	8.23 (6.41 to 10.57)	5.53 (4.26 to 7.19)	7.17 (5.37 to 9.59)
Likelihood of dependence in ADLs[b]	0.83 (0.36 to 1.93)	0.64 (0.35 to 1.14)	0.66 (0.25 to 1.79)
Zip code median income			
<$50 000	[Referent]	[Referent]	[Referent]
$50 000-$54 999	1.26 (0.88 to 1.79)	1.18 (0.80 to 1.76)	1.30 (0.86 to 1.95)
$55 000-$59 999	0.97 (0.66 to 1.43)	0.85 (0.55 to 1.31)	0.90 (0.57 to 1.44)
$60 000-$69 999	1.12 (0.82 to 1.54)	1.07 (0.75 to 1.51)	1.22 (0.85 to 1.75)
≥$70 000	1.00 (0.78 to 1.28)	0.99 (0.76 to 1.30)	1.00 (0.75 to 1.33)

[a]Logistic regression models were fit separately within each cohort. The EFR cohort comprised patients with a diagnosis of osteoporosis, osteopenia, or bone fracture before PCa diagnosis. The LFR cohort comprised the subset of the primary cohort that had no claims for osteoporosis, osteopenia, any SRE-defining event, or DEXA during the outcome period. ADL = activity of daily living; CI = confidence interval; DEXA = dual-energy x-ray absorptiometry; EFR = elevated fracture risk; LFR = lowest fracture risk; OR = odds ratio; PCa = prostate cancer; SRE = skeletal-related event.
[b]Faurot algorithm (28).

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provide benefit in mCSPC from the Cancer and Leukemia Group B (CALGB) 90202 trial was first presented in February 2013 (22). Therefore, BMA therapy before this date (eg, 2007-2012 within our study period) might not be characterized as overuse unequivocally, although NCCN guidelines recommended against use across the entire study period (21). We did not observe a decline in BMA use following CALGB 90202. In principle, the negative results of CALGB 90202—which studied zoledronic acid only, not denosumab—may have contributed to a relative decline in zoledronic acid vs denosumab that we did observe; however, the "switch" toward denosumab occurred primarily during 2010-2012—before CALGB 90202—suggesting that this trial was unlikely to have been a factor.

Several factors may have contributed to the increase in denosumab use. The drug's labeled indication includes all patients with metastatic PCa (14), even though guidelines recommend it only for mCRPC, the setting in which it has been evaluated (9). This discrepancy may create confusion among clinicians regarding whether denosumab is recommended for mCSPC, potentially resulting in inadvertent overuse. Additionally, a trial of denosumab found greater SRE reductions vs zoledronic acid in mCRPC; it is possible that providers are extrapolating this finding to mCSPC despite the absence of data for denosumab in this setting. From the practice perspective, subcutaneous administration of denosumab may consume less time and fewer resources than zoledronic acid, which requires an infusion chair for intravenous administration. Finally, denosumab use may be financially motivated, as the billing margin is substantially higher than for zoledronic acid. Such incentives contribute to the delivery of more expensive care across the oncology spectrum (35). Strategies to better align practice with patient value may include coverage policies that favor higher-value drugs (zoledronic acid, in this case) and payment models that decouple provider reimbursement from drug price.

This study has limitations as a consequence of the claims-based design. In addition to SRE prevention, oncology clinical practice guidelines recommend BMA therapy for patients with PCa who have osteoporosis or patients with osteopenia and high fracture risk according to the FRAX algorithm (6,36). If some patients are diagnosed clinically with osteoporosis or osteopenia without a billed claim for it, then they may have remained in our analytic cohort, resulting in an overestimate of BMA overuse (because BMA therapy would be appropriate for such patients), but this is unlikely to have meaningfully influenced our findings for several reasons. In deriving the primary cohort, when we removed patients with evidence of high fracture risk (those with osteoporosis, osteopenia, or prior fracture), 50% of the cohort was excluded; this is comparable to the estimated prevalence of low bone mineral density in the US population (41.8% in men aged 70-79 years, 53.1% in men aged ≥80 years) (37) and the proportion of men eligible for BMA therapy according to the National Osteoporosis Foundation guidelines (29.0% of men aged 70-79 years, 57.1% of men aged ≥80 years) (38). Additionally, we assessed the subset of patients who had no evidence of osteoporosis, osteopenia, an SRE-defining event, or DEXA bone density testing during the outcome period (LFR cohort); although this analysis should be interpreted with a high degree of caution because of the potential for reverse-causality, the relative similarity of BMA use between the LFR and primary cohorts suggests that newly discovered osteoporosis or osteopenia occurring after PCa diagnosis likely accounts for only a small portion of BMA use among patients with mCSPC. Finally, our assessment of dosing strength suggests that the majority of BMA therapy in this population is intended for SRE prevention rather than osteoporotic fracture prevention.

A separate limitation of claims is that castration sensitive vs resistant status is not available, and we aimed to study patients with mCSPC specifically. We addressed this limitation by applying an outcome period close enough to diagnosis that development of CRPC would be unlikely. A small fraction of patients may develop CRPC within this time frame, however, and appropriately receive BMA therapy in response. We assessed this possibility by measuring BMA use within 90 days, in which CRPC would be even more unlikely; the majority of BMA therapy began within 90 days, suggesting that in most cases the decision to administer BMAs was made soon after diagnosis and not in response to the early emergence of CRPC. In contrast, the 180-day outcome period may underestimate the proportion of patients who receive BMAs in the castration-sensitive setting because this approach would not identify patients who initiated BMA therapy later than 180 days but before castration resistance. Finally, the SEER–Medicare data set is limited to older adults residing in SEER regions and may not be generalizable to other populations.

Although BMAs are not recommended for patients with mCSPC, a substantial fraction receive them. The proportion of patients with mCSPC receiving BMAs increased following the 2010 approval of denosumab, while zoledronic acid use declined. Receipt of BMAs is associated with treatment in the physician office and by medical oncologists. Reducing BMA use within this population may reduce health care spending, patient out-of-pocket costs, and drug toxicity without adversely affecting patient outcomes.

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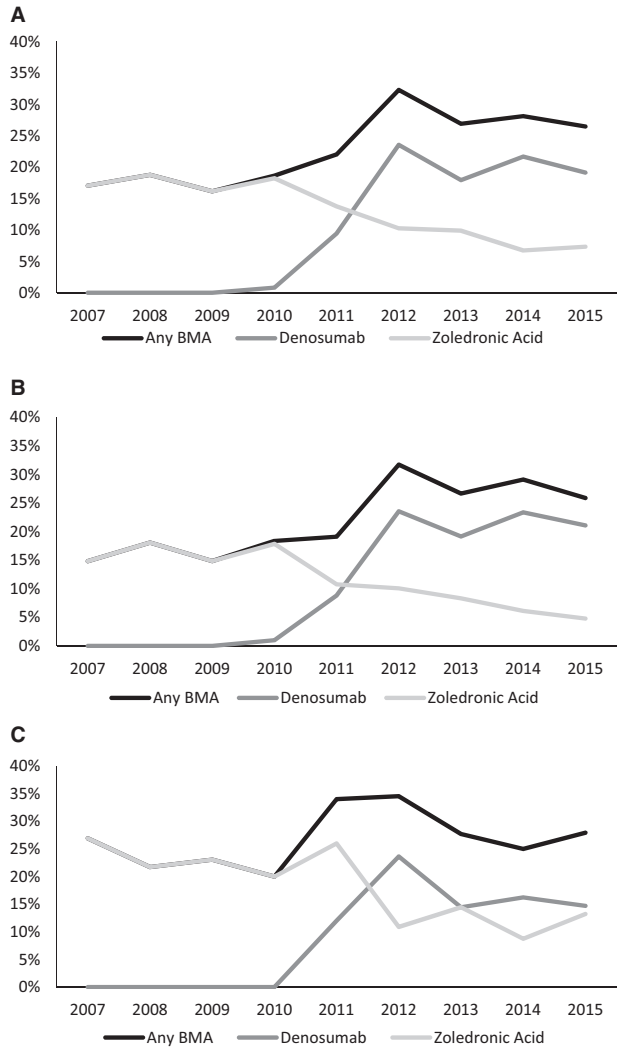

Figure 2. Receipt of any bone-modifying agent (BMA) within 180 days of diagnosis over time. Results for the overall primary cohort (N = 2827) (**A**), physician office setting (n = 2041) (**B**), and hospital outpatient setting (n = 586) (**C**) are shown.

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Data Availability

The data underlying this article were provided by the Centers for Medicare & Medicaid Services (CMS) under license. Data are available from CMS on request and establishment of data use agreement.

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