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RESEARCH ARTICLE

Incidence and prevention of skeletal-related events in multiple myeloma patients: A population-based real-world experience

Marie Røra[1,2] | **Margrete Skretting Solberg**[1,2] | **Kari Lenita Falck Moore**[3,4,5] | **Tobias S. Slørdahl**[1,2]

[1]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

[2]Department of Hematology, St. Olavs Hospital, Trondheim, Norway

[3]KG Jebsen Center for B cell malignancies, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[4]Department of Hematology, Oslo Myeloma Center, Oslo University Hospital, Oslo, Norway

[5]Department of Hematology and Oncology, Stavanger University Hospital, Stavanger, Norway

Correspondence
Tobias S. Slørdahl, Department of Haematology, St. Olavs hospital HF, Postboks 3250 Torgarden, 7006 Trondheim, Norway.
Email: tobias.s.slordahl@ntnu.no

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Abstract

Novel treatments in multiple myeloma (MM) could influence the incidence of skeletal-related events (SREs). We aimed to examine the incidence of SRE and the preventive use of osteoclast inhibitors (OIs) in a cohort of MM patients in the era of modern treatment. In this real-world retrospective study, we included 199 patients with a diagnosis of MM between January 1, 2010, and December 31, 2019, with follow-up at St. Olavs University Hospital. Data was extracted from The Myeloma Registry of Central Norway. SREs occurred in 46% of patients at baseline and 55.8% during follow-up. Excluding baseline SREs, the incidence rate was 29 (95% confidence interval: 26–33) per 100 person years. 48% experienced > 1 SRE. The incidence of SREs was highest at baseline followed by a gradual increase in each subsequent line of treatment. The first two years after diagnosis 80% received bisphosphonates (BPs). The proportion of recommended dosage was 46%. Only two cases (1.2%) of symptomatic hypocalcemia and one case (0.6%) of osteonecrosis of the jaw were identified. SREs are still a common problem in an era of novel treatment. Cumulative dosage of BPs was lower than recommended, and treatment with BPs was safe in this population.

KEYWORDS
bisphosphonates, Calcium and Vitamin D, denosumab, epidemiology, hypocalcemia, multiple myeloma, osteoclast inhibitors, osteonecrosis of the jaw, skeletal-related events

1 | INTRODUCTION

Multiple myeloma (MM) is a hematological malignancy in the bone marrow, with the proliferation of clonal plasma cells and the presence of monoclonal proteins in serum and/or urine. MM has the second-highest incidence among hematological malignancies [1]. The risk of developing MM increases with age, with a median age of onset of 71 years in the Norwegian population [2]. There is still no curative treatment, but the introduction of novel therapies has led to deeper treatment responses, better disease control, and improved survival [1–3]. In the population of the Nordic countries, survival has increased in all age groups, including the population above 75 years [2, 4].

MM differs from other hematological cancers in the destruction of bone in the proximity of cancer cells [5], and up to 80% of MM patients present with osteolytic bone lesions at diagnosis [6, 7]. The pathophysiology of MM bone disease (MBD) is the uncoupling of the bone-remodeling process caused by the malignant plasma cell [5, 7]. Bone lesions increase the risk of skeletal-related events (SREs), defined as pathological fractures, spinal cord compression, or the need for surgical or radiotherapeutic intervention [7, 8]. SREs can lead to

Marie Røra and Margrete Skretting contributed equally.

serious suffering for many patients, decrease quality of life (QoL), and impact overall survival [9, 10], along with increasing healthcare-associated costs [11]. Therefore, prevention of SREs is important and can be achieved by using osteoclast inhibitors (OIs), including bisphosphonates (BPs) or denosumab, a monoclonal antibody against RANK-ligand [12–15]. Two potential adverse drug events of OIs are hypocalcemia and osteonecrosis of the jaw (ONJ) [7, 16]. In a landscape where myeloma treatment improves rapidly and possibly also impacts MBD, our primary aim was to examine the incidence of SREs along with the use of OIs as both primary and secondary prophylaxis, in a cohort of Norwegian myeloma patients in the era of novel drugs.

2 | METHODS

2.1 | Data sources

Information on all MM cases was provided by The Myeloma Registry of Central Norway (MRCN). The MRCN has a coverage of > 95% of all patients with MM in the region. We included data on baseline characteristics, lines of myeloma treatment, progression, SREs, laboratory values, ONJ, and OI administration.

2.2 | Study population

In the study, we included all cases of MM (ICD-10: C90.00), with an entry in the MRCN and with follow-up at St. Olav University Hospital in the period January 1, 2010–December 31, 2019. Patients were followed until death or until a final cut-off of December 31, 2019. We excluded patients with the diagnosis of smoldering myeloma.

2.3 | Definitions

All SREs registered in the MRCN are based on a review of electronic health records. In the MRCN the SREs are defined in accordance with international guidelines [7, 8]. We classified SREs occurring within 60 days prior to or after MM diagnosis as baseline SREs. SREs were defined as the same event if they occurred within 21 days of each other and were in the same skeletal area (vertebral column, costae, sternum, clavicle, pelvis, cranium, upper or lower extremity), to ensure that interconnected events were not counted as distinct SREs. This definition is partly based on previous studies examining SREs in MM patients [17, 18]. For calculating the incidence rate in each treatment line, an SRE between two treatment lines was placed in the previous line's group unaffected by the termination of treatment. To investigate the correlation between SREs and the initiation of new treatment lines, we registered SREs occurring 30 days before or after starting a treatment line. Disease progression was defined according to the International Myeloma Working Group (IMWG) criteria [19].

Creatinine was registered at baseline and the estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 creatinine formula. We defined hypocalcemia as serum-corrected calcium < 2.20 mmol/L (< 8.8 mg/dL) [20, 21], and graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0 [22]. For the patients given BPs, we registered the lowest value of serum total calcium within the first 3 months after initiation if serum total calcium was below the lower reference range (<2.15 mmol/L) of the local laboratory. For patients with low serum total calcium, we registered serum albumin to calculate corrected calcium with the formula: serum calcium (mmol/L) + 0.02 (40 – serum albumin (g/L)) [20, 23]. Due to a lack of documented albumin value, serum total calcium was used in 18 patients while ionized calcium level was used in one patient.

To investigate the use of OIs, we registered the doses administered in the outpatient clinic. Records of calcium and vitamin D supplementation were incomplete. Therefore, supplementation was registered as present if mentioned in health records at any point, prior to or after MM diagnosis. Only two patients received Denosumab, one of them due to osteoporosis. Hence, they were excluded from analysis results regarding hypocalcemia and ONJ.

2.4 | Statistical methods

We used the statistical program SPSS (IBM statistics, version 28.0.1.0(142)) to perform descriptive analyses and Spearman's rank correlation to assess the relationship between cumulative dose of BPs and incidence of SREs. To adjust for different lengths of follow-up time in our correlation analyses, we calculated the percentage of recommended cumulative doses of BPs for the first 2 years (Norwegian guidelines 2012–2021), and the mean dose of BPs per month of the total follow-up time. For the variable "incidence of SREs", we excluded baseline SREs and calculated the mean number of SREs per month of follow-up after baseline. Bootstrapping was used for a 95% confidence interval (95% CI). The incidence rate was calculated by dividing the sum of SREs by the total follow-up time for the study population for the period of interest. Poisson Rate Confidence Interval was used for confidence intervals.

2.5 | Ethical approval

The project was approved by the Regional Committee for Medical and Health Research Ethics (399801) and the scientific committee of the MRCN. All living patients included in the MRCN have signed an informed consent for the use of their clinical data in medical research. We received an exemption from informed consent for patients who were dead at the time of inclusion in the MRCN.

3 | RESULTS

The baseline characteristics of the study population at diagnosis, including 199 patients, with a predominance of men, are shown in

TABLE 1 Baseline characteristics of the study sample. Follow-up time is calculated from 60 days after diagnosis to exclude the baseline period. For the detection of bone involvement at diagnosis, computed tomography (CT) has been the recommended modality since 2014. Before this, skeletal surveys were most commonly used. Estimated glomerular filtration rate (eGFR) is calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 creatinine formula. Hypercalcemia is defined as albumin-corrected calcium > 2.51 mmol/ L.

	Cohort ($n = 199$)
Sex, N (%)	
Male	121 (60.8)
Female	78 (39.2)
Age at diagnosis, years	
Median (range)	69 (34-92)
Follow-up length, months	
Median (range)	43 (0-143)
Previous low energy fracture, N (%)	26 (13.1)
Previous osteoporosis, N (%)	25 (12.6)
Previous treatment of osteoporosis, N (%)	24 (12.1)
Radiological findings at diagnosis, N (%)	
One or more osteolytic lesions	122 (61.3)
None	45 (22.6)
Unknown/ uncertain findings	32 (16.1)
Bisphosphonates within 3 months of diagnosis N (%)	114 (57.3)
Hemoglobin at diagnosis, g/dL	
Median (range)	11.3 (5.3–16.4)
eGFR at diagnosis, mL/min/1.73m^2	
Median (range)	79 (3–128)
Albumin corrected calcium at diagnosis, mmol/L	
Median (range)	2.39 (2.10–4.72)
Hypercalcemia, *N* (%)	56 (29.6)

Table 1. The median age at diagnosis was 69 years (range 34–92). The median follow-up time after the baseline period was 41 months (range 0–141). A previous history of low energy fracture and/or osteoporosis and/or treatment of osteoporosis was recorded in 13%, 13%, and 12%, respectively. Note that, 61% of patients had one or more osteolytic lesions on imaging at diagnosis. Treatment with BPs was started in 57% within three months of diagnosis (view Table 1 for further baseline characteristics).

3.1 | Skeletal-related events

During the study period, 348 SREs occurred, with a mean of 1.75 (95%CI: 1.51–2.01) events per patient. The incidence rate was 40 (95%CI: 36–45) per 100 person years (PYs). At least one SRE occurred in 143 of the 199 patients (72%) (Table 2). Only 28% recorded no SREs at all, while 48% experienced more than one SRE. 47% of SREs occurred during treatment, and 54% within 30 days before or after starting a new treatment line. Pathological fractures were the most frequent SRE and accounted for 70%, followed by radiation therapy (19%), and spinal cord compression (10%). Surgical treatment alone was rarely used (1%) (Figure 1). At baseline was the period with the highest occurrence of SREs (46%). The lowest incidence was found in treatment line 1, with an incidence rate of 18 (95%CI: 14–23), per 100 PYs, followed by a gradual increase to 148 (95%CI: 103–207) per 100 PYs in treatment line 6+. There was no significant difference between the groups of patients diagnosed in the time periods 2010–2014 and 2015–2019 (Figure 2). During follow-up, 34% of the patients who died, experienced an SRE after initiation of their final line of treatment. During the total follow-up time (baseline SREs excluded), SREs occurred in 55.8% of the study population, and the incidence rate was 29 (95%CI: 26–33) events per 100 PYs. The incidence rate was higher in patients ≥ 70 years at diagnosis, compared to < 70 years (Table 2).

3.2 | Osteoclast inhibitors

During the first 2 years after diagnosis, 159 of 199 patients (80%) received BPs, with a mean of 10 doses (95%CI: 9–11), ranging from 1–24. Several patients switched from Pamidronic acid (PA) to Zoledronic acid (ZA) during treatment. Two patients received Denosumab. Norwegian guidelines in the period 2012–2021 recommended monthly doses of OIs for the first 2 years (24 doses in total). The patients in our cohort received an average of 46.1% of this [24, 25]. Almost all the patients treated with BPs started within the first 2 years. During the complete time of follow-up, the mean total number of doses was 17 (95%CI: 15–19) for the entire population. The mean number of doses per month of follow-up was 0.43 (95%CI:0.39-0.47). The use of BPs is shown in Table 3. 7.4% experienced a dose reduction during treatment.

3.3 | Bisphosphonates and SREs

There was no statistically significant correlation between the cumulative dose of BPs in the first 2 years after diagnosis, and the incidence of SREs ($r = 0.06$, $N = 159$, $p = 0.447$) when only patients receiving BPs were included. However, there was a weak, but significant, positive correlation between a higher cumulative dose of BPs given during the total follow-up time, and a higher incidence of SREs ($r = 0.18$, $N = 162$, $p = 0.019$). When the whole study population was included, there was a weak, but statistically significant positive correlation between a higher incidence of SREs and a higher cumulative dose of BPs during the first 2 years after diagnosis ($r = 0.18$, $N = 199$, $p = 0.009$). This correlation also held true for the entire population for the total follow-up time ($r = 0.29$, $N = 199$, $p = < 0.001$).

TABLE 2 Incidence of skeletal-related events (SREs) in a clinical cohort of multiple myeloma patients, $n = 199$. Baseline is defined as the period 60 days prior to and after diagnosis. SREs were defined as the same event if they occurred within 21 days of each other and were in the same skeletal area (vertebral column, costae, sternum, clavicle, pelvis, cranium, upper or lower extremity), to ensure that interconnected events were not counted as distinct SREs.

	Total (95% CI)	Baseline excluded (95% CI)
Sum ($N = 199$)	348	233
Mean	1.75 (1.51–2.01)	1.18 (0.97–1.40)
Incidence rate (total), per 100 PYs	40 (36–45)	29 (26–33)
< 70 years ($N = 103$)	36 (31–41)	26 (22–31)
≥ 70 years ($N = 96$)	48 (41–56)	34 (28–42)

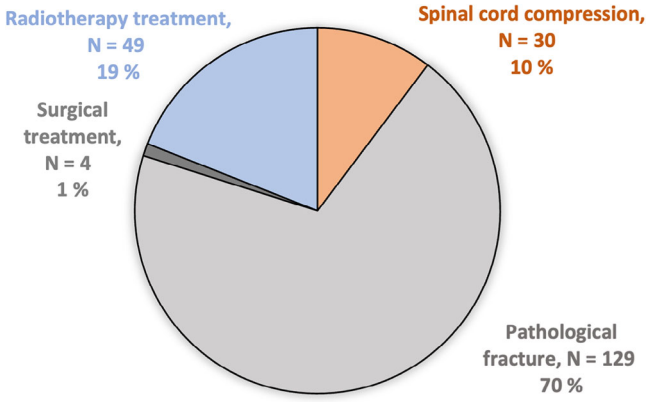

FIGURE 1 Distribution of skeletal-related events (SREs) by type in a clinical cohort of multiple myeloma patients, $n = 199$. N = number of patients experiencing each type.

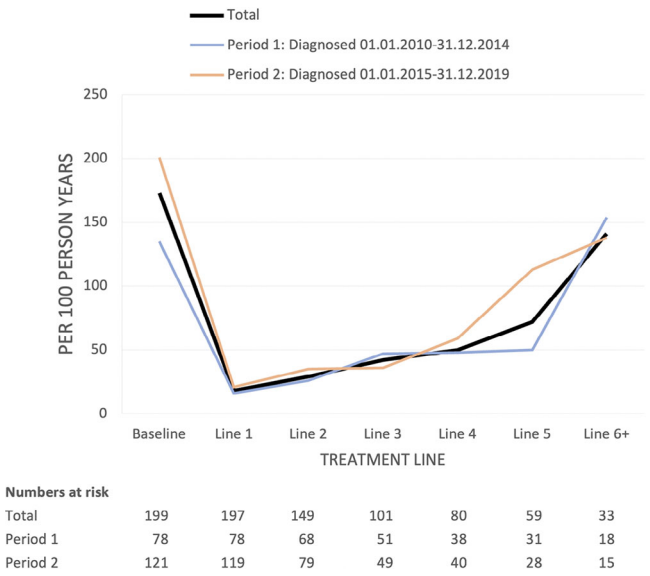

FIGURE 2 Incidence rate of skeletal-related events (SREs) by treatment line. The baseline includes SREs 60 days prior to or after diagnosis. Due to overlapping time periods, baseline SREs that occurred in line 1 were counted as baseline and subtracted from line 1. SREs in line one are intended to represent SREs occurring despite myeloma treatment. The time period for each treatment line was calculated from the start treatment line until the start next treatment line, a final cut-off of (December 31, 2021) or death.

3.4 | Calcium and osteonecrosis of the jaw

Calcium supplementation with or without vitamin D was mentioned in the charts of 20% of the patients included in this study. For the remaining 80%, supplements were not mentioned at all. In 53 patients (33%) given BPs, we found calcium below the reference range within 3 months of starting BP therapy. According to CTCAE 5.0, most of these cases (45) were mild. One event was grade 4 based on laboratory values, although the patient did not have any symptoms. Only two symptomatic cases with the need for treatment were identified. The incidence rate of hypocalcemia was 131 (95%CI: 98–171) per 100 PYs. ONJ occurred in one patient (0.6%). (Table 4).

4 | DISCUSSION

In this real-world retrospective cohort study, we investigated the incidence of SREs and the use of BPs in a clinical cohort of 199 patients with MM and follow-up at St. Olav's Hospital. Baseline SREs occurred in almost half of the patients. During the follow-up time (baseline excluded), SREs occurred in 56% of the study population. Pathological fractures were the most frequent type and accounted for 70% of the cases. 48% experienced more than one SRE, and 54% of SREs occurred 30 days before or after starting a new treatment line. The incidence of SREs increased in later treatment lines. During the first 2 years after diagnosis, the majority (80%) of the MM patients received BPs. The proportion of recommended dosage was 46%. A higher cumulative dose of BPs was not associated with a reduction in the incidence of SREs. Most of the MM patients did not receive any documented supplementation with calcium and/or vitamin D as part of their treatment. Only two cases of hypocalcemia requiring treatment were identified and one case of ONJ.

The incidence of SREs found in our study is in line with other real-world studies from the USA, Greece, and the Republic of Korea [11, 17, 26, 27]. Similar to our study, others have also found that pathological fractures are the most frequent type of SREs [17, 26, 28]. Further, alongside results from Baek et al., we also found a trend of more SREs in patients aged 70 years and older [18]. Interestingly, nearly 50% of the SREs did not occur in relation to starting a new line of treatment. This is probably due to fractures not being judged as disease

TABLE 3 Use of bisphosphonates during the first two years after diagnosis and for the total follow-up time. The percentage of recommended doses is based on Norwegian guidelines (2012–2021), which recommend BPs monthly for the first 2 years after diagnosis. 100% corresponds to one dose per month of follow-up for up to 2 years. Patients dying within the first 2 years were included, and shorter follow-up time was adjusted for.

	N (%)	Mean (95%CI)	Minimum/maximum number of doses
First 2 years			
Total number of doses with BPs	**159 (79.9)**	**10.0 (9.1–11.0)**	**1–24**
Zoledronic acid	**88 (44.2)**		
Number of doses		9.2 (7.7–10.8)	1–24
Cumulative dose (1 dose = 4 mg)		38.4 (31.8–45.3)	4.0–176.0 mg
Pamidronic acid	**104 (52.3)**		
Number of doses		8.0 (7.0–9.0)	1–20
Cumulative dose (1 dose = 30 mg)		239.4 (208.0–272.0)	15.0–690.0 mg
Proportion of recommended dosage		**46.1% (42.0%–50.4%)**	**4.2%–100%**
Total follow-up time			
Total number of doses of BPs	**162 (81.4)**	16.7 (14.9–18.5)	1–42
Zoledronic acid	**110 (55.3)**		
Number of doses		13.8 (11.9–15.8)	1–37
Cumulative dose (1 dose = 4 mg)		54.4 (46.5–62.2)	4.0–148.0 mg
Pamidronic acid	**104 (52.3)**		
Number of doses		11.7 (10.0–13.3)	1–33
Cumulative dose (1 dose = 30 mg)		350.5 (299.1–401.0)	15.0–990 .0 mg
Mean number of doses/ months		**0.43 (0.39–0.47)**	**0-1.1**

TABLE 4 Frequency of calcium and vitamin D supplementation, hypocalcemia, and osteonecrosis of the jaw. Supplementation was registered as yes if given at some point, prior to or after diagnosis. Both calcium alone and combined with vitamin D were registered. Hypocalcemia was defined as albumin-corrected calcium < 2.20 mmol/L and graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0. The case of osteonecrosis of the jaw was CTCAE grade 3.

	Yes, *N* (%)	No, *N* (%)
Calcium and vitamin D supplementation	**40 (20)**	**159 (80)**
Hypocalcemia within 3 months after start of BPs	**53 (33)**	**109 (67)**
CTCAE Grade 1 (mild)	45	
CTCAE Grade 2 (moderate)	5	
CTCAE Grade 3 (severe)	2	
CTCAE Grade 4 (life-threatening)	1	
CTCAE Grade 5 (death)	0	
Osteonecrosis of the jaw	**1 (0.6)**	**161 (99.4)**

progression by the treating physician. Since regular CT scans are not standard follow-up in myeloma, we do not know if these SREs were preceded by progressive bone disease. A recent study by the Nordic Myeloma Study Group (NMSG) indicates that regular pre-planned bone imaging can identify progressive bone disease earlier than standard follow-up today [29].

Almost half of our study population experienced more than one SRE. This is consistent with other studies that suggest having a history of SREs increases the risk of new events [17, 28]. The highest proportion of SREs were found during the baseline period followed by a low occurrence in treatment line 1. This aligns with previous studies showing that most bone complications occur early in the disease course [13, 17, 28]. In addition, we found a gradual increase in SREs from treatment lines 1–6+, consistent with the database study from oncology clinics in the United States showing an increase in SREs with each subsequent line [17].

In our study, BPs were given to 80% of the patients, which is higher than in comparable cohorts in Denmark [30] and the Republic of Korea

[27], but similar to the chart review of 5 European countries by Mateos et al. [28]. ZA was the most frequently used BP in our cohort, consistent with guidelines from 2015 [31], recommending ZA as the first option, due to superior overall survival (OS) compared to clodronate [12].

Our population received fewer doses of BPs than recommended by the Norwegian guidelines. This may be influenced by changes in recommendations during the inclusion period. The first national guidelines were published in 2012 and recommended PA 30 mg every 4 weeks or ZA 4 mg every 4 weeks for up to 2 years for patients with MBD. From 2015, ZA was recommended as the first option for all patients for up to 2 years due to the documented increase in OS [32]. From 2020 treatment with ZA was recommended to continue for 2 years (24 doses in total) [24, 25]. Discontinuation of BPs due to a decrease in kidney function may be another reason for the low number of doses. BPs are not recommended for patients with eGFR below 30 mL/min, and in this group, Denosumab is a reasonable option due to its extrarenal clearance [8]. Denosumab was first recommended in Norwegian guidelines in 2018 [33]. Overall, 20% had no record of treatment with BPs and only 2 patients received Denosumab. This suggests an unmet need, especially in patients with reduced kidney function or lack of detectable bone disease.

Previous randomized controlled studies have found that increasing the amount of BPs leads to a reduction of SREs [34]. Recent results from the MAGNOLIA study (NMSG 22/14) showed a reduced number of SREs with 4 years compared to 2 years of treatment with ZA, indicating a preventive effect of more doses of BPs [35]. In our study, a higher cumulative dose of BPs was associated with more SREs, most pronounced in the analysis including the whole study population. This association is most likely biased and due to confounding where the patients with more SREs were more likely to be given BPs. National guidelines recommend reinitiating BPs with relapse of active bone disease, and up to 2015 BPs were only recommended in patients with MBD [24]. Our results also suggest a low incidence of SREs among patients not treated with BPs, supporting the physician's decision to abstain from treatment. Despite explicit national guidelines, there are still different opinions concerning treatment with BPs in patients without detectable MBD.

Supplementation with calcium was only mentioned in the health records of 20% of patients. The IMWG and the European Society for Medical Oncology recommend supplementation to all patients receiving OIs to prevent hypocalcemia [7, 8] However, Norwegian guidelines have not yet mentioned supplementation [24]. In concordance with other studies, we found only two symptomatic cases of hypocalcemia. Previous studies show varying results regarding the occurrence of hypocalcemia with the use of BPs and the preventive effect of calcium supplementation [36, 37, 38]. Our study supports the finding that hypocalcemia is rarely a clinically significant complication of BP use, even when the use of calcium supplementation is low.

ONJ occurred in only one patient (0.6%) during this study, a lower occurrence than seen in clinical trials. [13]. Results from an open-label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer [39], found higher rates of ONJ with increased exposure to anti-resorptive treatment. The low incidence of ONJ in our cohort may be affected by our population receiving a relatively low number of doses of BPs compared to recommendations and clinical trials. In addition, patients in our study were not systematically checked for ONJ, which may also be a contributing factor to the low incidence.

Our study encompassed many unique features and strengths. Our study is a robust real-world study including a population-based cohort representative of the total MM population, including elderly patients, those with comorbidities, and patients who died shortly after diagnosis. The MRCN includes SREs based on a thorough medical record review, not diagnostic or treatment coding. Due to different methods, definitions of SREs, populations, and data sources in the studies on SREs in MM patients, the incidence rates and proportions may not be directly comparable. Limitations include human error and incomplete documentation.

In conclusion, this study found a high incidence of SREs in a cohort treated during the recent decade, with access to novel drugs. The incidence was highest at baseline and increased again in later treatment lines. A high proportion of patients received OIs, but the number of doses was lower than National recommendations, and few patients received Denosumab. The use of BPs was safe with few cases of clinical hypocalcemia and ONJ. In the future, studies comparing BP treatment with different dosages and dosing intervals may lead to fewer side effects, lower costs, and less time use for patients and health services (Supporting Tables).

AUTHOR CONTRIBUTIONS

All authors designed the study. Marie Røra and Margrete Skretting Solberg collected and analyzed data and wrote the manuscript. Marie Røra performed the statistical analysis. All authors interpreted the data and critically revised, discussed, and approved the last version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Marie Røra, Margrete Skretting Solberg, and Kari Lenita Falck Moore declare no conflict of interest. Tobias S. Slørdahl has received honoraria from Takeda, Celgene, Amgen, Abbvie, and Janssen-Cilag. Consultancy: Bristol Myers Squibb and GSK. Advisory board consultancy: Amgen, Celgene, GSK, and Janssen-Cilag.

DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The project was approved by the Regional Committee for Medical and Health Research Ethics (399801) and the scientific committee of the MRCN. All living patients included in the MRCN have signed an

informed consent for the use of their clinical data in medical research. We received an exemption from informed consent for patients who were dead at the time of inclusion in the MRCN.

PATIENT CONSENT STATEMENT

All living patients included in the MRCN have signed an informed consent for the use of their clinical data in medical research. We received an exemption from informed consent for patients who were dead at the time of inclusion in the MRCN.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

ORCID

Kari Lenita Falck Moore https://orcid.org/0000-0002-2190-2762
Tobias S. Slørdahl https://orcid.org/0000-0001-7488-4863

REFERENCES

1. Turesson I, Bjorkholm M, Blimark CH, Kristinsson S, Velez R, Landgren O. Rapidly changing myeloma epidemiology in the general population: Increased incidence, older patients, and longer survival. E J Haematol. 2018;101(2):237–44.
2. Langseth ØO, Myklebust TÅ, Johannesen TB, Hjertner Ø, Waage A. Incidence and survival of multiple myeloma: a population-based study of 10 524 patients diagnosed 1982–2017. Br J Haematol. 2020;191(3):418–25.
3. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol. 2010;28(5):830–34.
4. Moore KLF, Turesson I, Genell A, Klausen TW, Knut-Bojanowska D, Redder L, et al. Improved survival in myeloma patients–a nationwide registry study of 4647 patients 75 years treated in Denmark and Sweden. Hematologica. 2023;108(6):1640–51.
5. Børset M, Sundan A, Waage A, Standal T. Why do myeloma patients have bone disease? A historical perspective. Blood Rev. 2020;41:100646.
6. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21–33.
7. Terpos E, Zamagni E, Lentzsch S, Drake MT, García-Sanz R, Abildgaard N, et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. Lancet Oncol. 2021;22(3):e119–30.
8. Terpos E, Kleber M, Engelhardt M, Zweegman S, Gay F, Kastritis E, et al. European Myeloma Network Guidelines for the management of multiple myeloma-related complications. Haematologica. 2015;100(10):1254–66.
9. Jordan K, Proskorovsky I, Lewis P, Ishak J, Payne K, Lordan N, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. Support Care Cancer. 2014;22(2):417–26.
10. Sonmez M, Akagun T, Topbas M, Cobanoglu U, Sonmez B, Yilmaz M, et al. Effect of pathologic fractures on survival in multiple myeloma patients: a case control study. J Exp Clin Cancer Res. 2008;27(1):11.
11. Nash Smyth E, Conti I, Wooldridge JE, Bowman L, Li L, Nelson DR, et al. Frequency of skeletal-related events and associated healthcare resource use and costs in US patients with multiple myeloma. J Med Econ. 2016;19(5):477–86.
12. Morgan GJ, Child JA, Gregory WM, Szubert AJ, Cocks K, Bell SE, et al. Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. Lancet Oncol. 2011;12(8):743–52.
13. Raje N, Terpos E, Willenbacher W, Shimizu K, García-Sanz R, Durie B, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol. 2018;19(3):370–81.
14. Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet. 2010;376(9757):1989–99.
15. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med. 1996;334(8):488–93.
16. Gimsing P, Carlson K, Turesson I, Fayers P, Waage A, Vangsted A, et al. Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. Lancet Oncol. 2010;11(10):973–82.
17. Kim C, Bhatta S, Cyprien L, Fonseca R, Hernandez RK. Incidence of skeletal-related events among multiple myeloma patients in the United States at oncology clinics: Observations from real-world data. J Bone Oncol. 2019;14:100215.
18. Baek YH, Jeon HL, Oh IS, Yang H, Park J, Shin JY. Incidence of skeletal-related events in patients with breast or prostate cancer-induced bone metastasis or multiple myeloma: A 12-year longitudinal nationwide healthcare database study. Cancer Epidemiol. 2019;61:104–10.
19. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328–3e46.
20. Correcting the calcium. Br Med J (Clin Res Ed). 1977;1(6061):598.
21. Shrimanker I, Bhattarai S. Electrolytes. Treasure Island (FL): StatPearls Publishing; 2023.
22. Institute NC. Common Terminology of Adverse Events (CTCAE). 2021.
23. Lian IA, Åsberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. BMJ Open. 2018;8(4):e017703.
24. Helsedirektoratet. Nasjonalt handlingsprogram for maligne blodsykdommer. 2021.
25. Helsedirektoratet. Nasjonalt handlngsprogram for maligne blodsykdommer. 2013.
26. Kanellias N, Ntanasis-Stathopoulos I, Gavriatopoulou M, Koutoulidis V, Fotiou D, Migkou M, et al. Newly diagnosed multiple myeloma patients with skeletal-related events and abnormal MRI pattern have poor survival outcomes: a prospective study on 370 patients. J Clin Med. 2022;11(11):3088.
27. Lee JY, Lee JH, Kim S-A, Suh KJ, Kim J-W, Kim SH, et al. Incidence of skeletal-related events among multiple myeloma patients: a nationwide population-based cohort study. Blood. 2022;140(Supplement 1):12570.
28. Mateos M-V, Fink L, Koneswaran N, Intorcia M, Giannopoulou C, Niepel D, et al. Bone complications in patients with multiple myeloma in five European countries: a retrospective patient chart review. BMC Cancer. 2020;20(1):170.
29. Gundesen MT, Asmussen JT, Schjesvold F, Vangsted AJ, Helleberg C, Haukås E, et al. Potential value of pre-planned imaging of bone disease in multiple myeloma. Blood Cancer J. 2023;13(1):105.

30. Olesen TB, Andersen IT, Ording AG, Ehrenstein V, Seesaghur A, Helleberg C, et al. Use of bisphosphonates in multiple myeloma patients in Denmark, 2005–2015. Support Care Cancer. 2021;29(8):4501–11.
31. Helsedirektoratet. Nasjonalt handlingsprogram for maligne blodsykdommer. 2015.
32. Sanfilippo KM, Gage B, Luo S, Weilbaecher K, Tomasson M, Vij R, et al. Comparative effectiveness on survival of zoledronic acid versus pamidronate in multiple myeloma. Leuk Lymphoma. 2015;56(3):615–21.
33. Helsedirektoratet. Nasjonalt handlingsprogram for maligne blodsykdommer. 2018.
34. Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Bisphosphonates in multiple myeloma: an updated network meta-analysis. Cochrane Database Syst Rev. 2017;2017(12).
35. Lund. Abstract OA10 at 20th IMS Annual Meeting. 2023.
36. Yerram P, Kansagra S, Abdelghany O. Incidence of hypocalcemia in patients receiving denosumab for prevention of skeletal-related events in bone metastasis. J Oncol Pharm Pract. 2017;23(3):179–84.
37. Chennuru S, Koduri J, Baumann MA. Risk factors for symptomatic hypocalcaemia complicating treatment with zoledronic acid. Intern Med J. 2008;38(8):635–37
38. Body J-J, Bone HG, de Boer RH, Stopeck A, Van Poznak C, Damião R, et al. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. Eur J Cancer. 2015;51(13):1812–21.
39. Stopeck AT, Fizazi K, Body JJ, Brown JE, Carducci M, Diel I, et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Support Care Cancer. 2016;24(1):447–55.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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