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ORIGINAL ARTICLE

# Use of anti-osteoporosis medication dispensing by patients with hip fracture: could we do better?

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## Abstract

**Summary** Although Scandinavian countries have the highest incidence of hip fracture in the world, trends in anti-osteoporosis medication use have not been studied. We found less than one-third of Danish hip fracture patients had dispensing of anti-osteoporosis medication over a 10-year period using routinely collected data from population-based registries.

**Introduction** To examine trend in dispensing of anti-osteoporosis medication before and after hip fracture surgery in Denmark over a 10-year period using routinely collected data from population-based registries.

**Methods** From the Danish Multidisciplinary Hip Fracture Registry, we included 65,011 patients aged 65 years or older with an incident hip fracture in 2005–2015. We calculated, for each calendar year of hip fracture diagnosis, the prevalence of use of anti-osteoporosis medication (at least one dispensing of bisphosphonates, strontium ranelate, denosumab, selective estrogen receptor modulators, or teriparatide) in the year before and in the year following hip fracture diagnosis. Among those without a dispensing in the year before hip fracture, we computed 1-year cumulative incidence of use following hip fracture. We treated death as a competing risk and stratified the analysis on sex, age, and comorbidity.

**Results** The prevalence of use before hip fracture varied between 7 and 12%, increasing slightly from 2005 to 2015. The cumulative incidence of use following hip fracture decreased from 16% in 2005 to 13% in 2010, whereupon it increased to 20%. A similar pattern was seen with each stratum of sex, age groups, and comorbidity. The overall prevalence of use after hip fracture was below 22% in all calendar years.

**Conclusions** Less than one-third of hip fracture patients had dispensing of anti-osteoporosis medication up to 1 year after hip fracture. We observed only a slight increase in dispensing after hip fracture over the study period, irrespective of patient sex, age, and comorbidity at the time of hip fracture.

**Keywords** Anti-osteoporosis medication · Bisphosphonates · Hip fracture · Osteoporosis · Trend

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00198-019-05066-8) contains supplementary material, which is available to authorized users.

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## Introduction

Osteoporosis affects over 200 million people worldwide [1], manifesting as nearly 9 million fractures, including fractures in the hip, spine, and distal forearm [2]. Sustaining a hip fracture more than triples the risk of a subsequent fracture, with the highest risk concentrated within the first post-fracture year [3–5]. Among patients with hip fracture, bisphosphonates are an effective [6], but potentially underutilized, treatment for secondary fracture prevention [7–13], with less than one-third of these patients receiving treatment [14, 15]. The 2008 Guidelines of the UK's National Institute for Health and Clinical Excellence (NICE) recommend the use of anti-osteoporosis medication including bisphosphonates, raloxifene, teriparatide, or strontium ranelate for secondary fracture

prevention for all hip fracture patients [16]. In September 2018, the American Society for Bone and Mineral Research recommended that people above 65 years who have a hip or spine fracture should be treated for osteoporosis [17]. Following publication of the NICE guidelines, studies investigating the period up to 2013 have shown an increase in initiation of treatment for secondary prevention after hip fracture, especially among women older than 75 years [18, 19]. Nevertheless, the overall treatment initiation rates remained unchanged at 34% in 1999–2013 [19]. Data from the Scandinavian countries on recent trends in utilization of anti-osteoporosis medication for secondary fracture prevention can be accessed in national country statistics [20], but have not been summarized in peer review publications, despite their world's highest incidence of hip fracture (average age-standardized annual rate is 346/100,000 in Denmark compared with 123/100,000 in Spain) [21, 22]. The Danish Ministry for Health has estimated that up to 70% of the hip fracture patients may benefit from secondary fracture prevention through anti-osteoporosis medication [23]. Furthermore, pre-fracture comorbidity is associated with an additional mortality risk [24, 25]. Therefore, it is relevant to examine anti-osteoporosis treatment both overall and in the context of existing comorbidity.

We examined time trends in dispensing of anti-osteoporosis medications before and after hip fracture in Denmark, overall, and stratified for sex, age, and comorbidity.

## Methods

We conducted this population-based descriptive cohort study in Denmark, a country with 5.7 million inhabitants, with universal access to medical care including partial reimbursement of prescription drug costs.

### Study population and data sources

Patients were identified in the Danish Multidisciplinary Hip Fracture Registry, which is a nationwide population-based clinical quality database, established in 2003 [26]. The database records all patients at age 65 years or older with hip fracture and contains detailed data on patient characteristics and in-hospital performance indicators. We included patients with an incident hip fracture who underwent surgery with arthroplasty or internal fixation from 2005 to 2015 ($n$ = 65,011). Patients with a diagnosis of hip fracture between 2003 and 2005 were excluded. We set the date of hip fracture surgery to indicate the date of hip fracture. To the study population, we linked data from the Danish Civil Registration System (personal identifier for linkage, migrations, and vital status) [27], the Danish National Patient Registry (inpatient and outpatient hospital diagnoses) [28], and the Danish National Health Services Prescription Database (outpatient dispensing) [29].

### Anti-osteoporosis medication dispensing

Anti-osteoporosis medication use was defined as at least one dispensing of an anti-osteoporosis medication (bisphosphonates including combinations, strontium ranelate, denosumab, selective estrogen receptor modulators, or teriparatide). We identified all anti-osteoporosis medication dispensing in the year before hip fracture and in the year after hip fracture. Switching between different types of anti-osteoporosis medications was not considered treatment termination. We classified patients as users of anti-osteoporosis medications in the 12 months before and in the 12 months after hip fracture, defined as at least one dispensing in the respective time window (Fig. 1). To characterize utilization, we classified pre-fracture use as either consistent use or intermittent use. Consistent use was defined based on at least one dispensing within each 6-month time window 12 months before hip fracture or based on a dispensing in the first time 6-month window that continued into the second 6-month time window, based on the number of defined daily doses plus a 90-day grace period. Intermittent users was defined as at least one dispensing in only one of the two 6-month time windows in the 12 months before hip fracture or if the days in the first period did not continue in the second period (Fig. 1). With respect to post-fracture use of anti-osteoporosis medications, we defined continuous use as any use both 12 months before and 12 months after hip fracture. Incident use was defined among non-users in the 12 months before hip fracture as use in the 12 months after hip fracture.

### Patient characteristics

We describe the study population in terms of sex, age at hip fracture date (categories 65–74 years, 75–84 years, and 85 years or older), body mass index (BMI) (underweight (BMI < 18.5 kg/m$^2$), normal weight (BMI 18.5–24.9 kg/m$^2$), overweight (25–29.9 kg/m$^2$), and obese (≥ 30 kg/m$^2$)), and fracture type according to the criteria used at the Danish Multidisciplinary Hip Fracture Registry (undisplaced femoral neck, displaced femoral neck, unspecified femoral neck, pertrochanteric and subtrochanteric). We also summarized the 10-year pre-fracture hospital comorbidity history using the Charlson Comorbidity Index (CCI) [28]: a score of 0 (low), given to patients with no previous record of diseases included in the CCI; a score of 1–2 (medium); and a score of 3 or more (high).

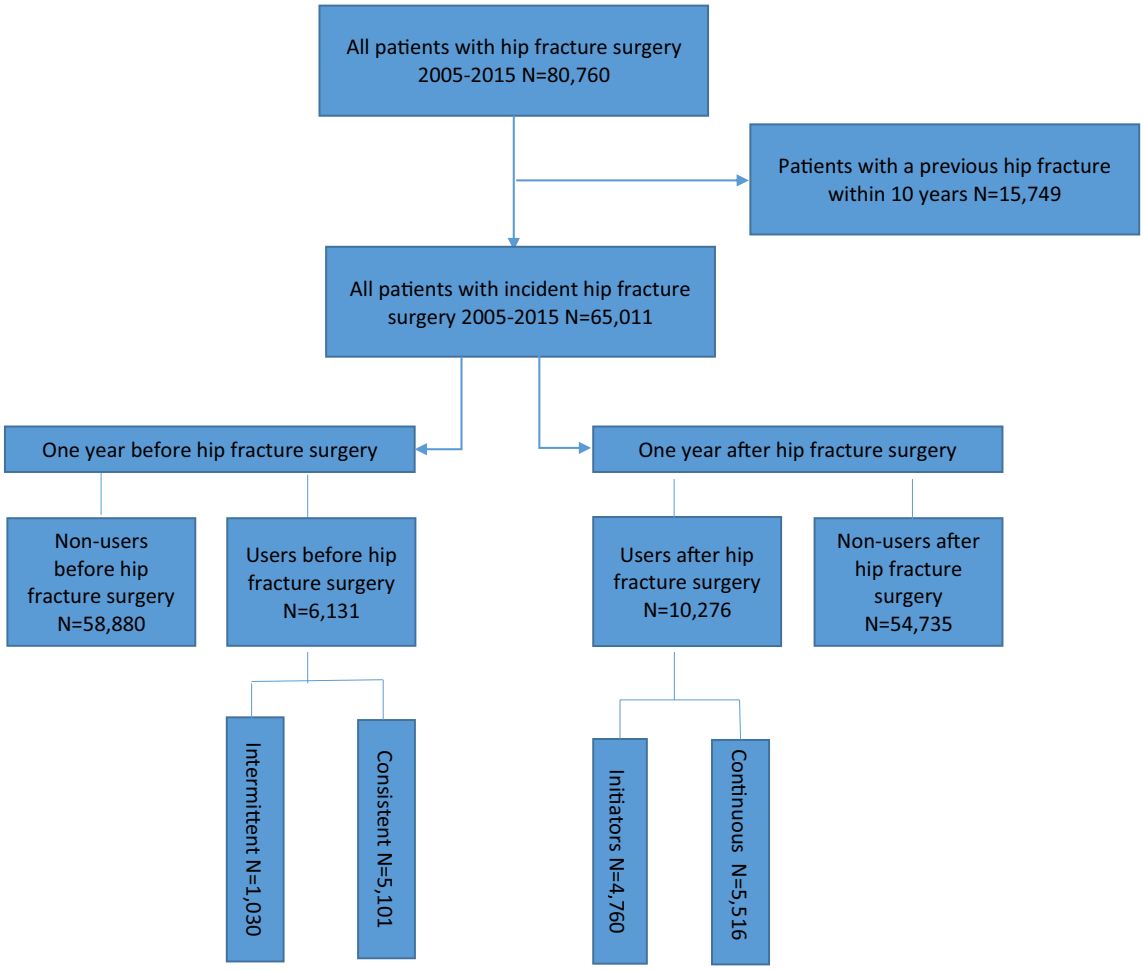


**Fig. 1** Flowchart for inclusion

### Statistical analysis

We tabulated the patients' characteristics overall and by the use of anti-osteoporosis medication before and after hip fracture and presented the distribution of use of different classes of anti-osteoporosis medications among the users. Pre-fracture use was expressed by 12-month prevalence proportion in the entire study population. Among pre-fracture non-users, we reported post-fracture 12-month incidence proportion of treatment initiation and, given the high post-fracture mortality, the 12-month cumulative incidence of treatment initiation following hip fracture treating death as a competing risk. Continuous use was expressed as a 12-month prevalence proportion among pre-fracture users. Measures of use were reported overall and stratified by calendar year of hip fracture, sex, age groups, CCI score, and previous fracture within 10 years from index date.

Supplement Appendix 1 lists the Anatomical Therapeutic Chemical Classification (ATC), International Classification of Diseases 10th revision codes (ICD-10) and Nordic Medico-Statistical Committee (NOMESCO) surgical procedure codes used in this study. The study was approved by the Danish Data Protection Agency (Aarhus University record number 2016-051-000001). Data analyses were performed using SAS version 9.4.

## Results

Among the 65,011 hip fracture patients, the prevalence of pre-fracture use of anti-osteoporosis medications was 9%, and 83% of the users were consistent users. Compared with non-users, both pre- and post-fracture users of anti-osteoporosis medications were older and more likely to be female, to have moderate comorbidity, to be underweight, or to have sustained a pertrochanteric or subtrochanteric hip fracture (Table 1). Among the post-fracture users, 54% were continuous users and 46% were incident users. Compared with the continuous users, the incident users had a higher proportion of men, were younger, and had a lower comorbidity burden. In addition, continuous users often had a femoral neck fracture and had had a previous fracture. Bisphosphonate was the only anti-

**Table 1** Demographics and clinical characteristics of the 65,011 patients with hip fracture

| | Overall | | After hip fracture | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $N = 65,011$ | | Users, 16% (10,276) | | | | Non-users, 84% (54,735) | |
| | | | Incident users, 46% (4760) | | Continuous users, 54% (5516) | | | |
| Sex | | | | | | | | |
| Men | 29% | 18,644 | 23% | 1075 | 10% | 551 | 69% | 37,717 |
| Women | 71% | 46,367 | 77% | 3685 | 90% | 4965 | 31% | 17,018 |
| Age groups | | | | | | | | |
| 65–74 years | 19% | 12,503 | 27% | 1274 | 18% | 982 | 19% | 10,247 |
| 75–84 years | 39% | 25,214 | 45% | 2137 | 44% | 2453 | 38% | 20,624 |
| ≥ 85 years | 42% | 27,294 | 28% | 1349 | 38% | 2081 | 44% | 23,864 |
| Charlson Comorbidity Index score | | | | | | | | |
| Low 0 points | 41% | 26,561 | 48% | 2271 | 34% | 1883 | 41% | 22,407 |
| Moderate 1–2 points | 40% | 26,127 | 38% | 1801 | 46% | 2524 | 40% | 21,802 |
| High 3 points | 19% | 12,323 | 14% | 688 | 20% | 1109 | 19% | 10,526 |
| Fracture diagnosis | | | | | | | | |
| Femoral neck | 53% | 34,428 | 56% | 2642 | 41% | 2281 | 54% | 29,505 |
| Per- and subtrochanteric | 47% | 30,583 | 44% | 2118 | 59% | 3235 | 46% | 25,230 |
| Surgery type | | | | | | | | |
| Osteosyntheses | 69% | 44,915 | 69% | 3269 | 76% | 4205 | 68% | 37,441 |
| Total and hemiarthroplasty | 31% | 20,096 | 31% | 1491 | 24% | 1311 | 32% | 17,294 |
| Body mass index | | | | | | | | |
| Underweight | 9% | 5556 | 7% | 355 | 13% | 721 | 8% | 4480 |
| Normal weight | 46% | 29,702 | 49% | 2347 | 49% | 2688 | 45% | 24,667 |
| Overweight | 20% | 12,844 | 22% | 1042 | 15% | 849 | 20% | 10,953 |
| Obese | 5% | 3531 | 7% | 323 | 4% | 197 | 6% | 3011 |
| Missing | 21% | 13,378 | 15% | 693 | 19% | 1046 | 21% | 11,624 |
| Cohabiting status | | | | | | | | |
| Living with a partner | 30% | 19,327 | 36% | 1729 | 27% | 1494 | 29% | 16,104 |
| Living alone | 70% | 45,678 | 64% | 3031 | 73% | 4022 | 71% | 38,625 |
| Missing | 0% | 6 | 0% | 0 | 0% | 0 | 0% | 6 |
| Previously fracture | | | | | | | | |
| No | 78% | 50,837 | 76% | 3640 | 66% | 3615 | 80% | 43,582 |
| Yes | 22% | 14,174 | 24% | 1120 | 34% | 1901 | 20% | 11,153 |

osteoporosis medication class used and will therefore be described further.

The prevalence of pre-fracture bisphosphonate use increased from 7% among patients with hip fracture in 2005 to 10% among patients with hip fracture in 2015 (Fig. 2). Patients with hip fracture in 2013 had the highest prevalence of pre-fracture use of 12%. Alendronate accounted for 83% of use; etidronate for 11% of use; and ibandronate, risedronate, and zoledronate together for 6% of use. There was no overall dispensing of other bisphosphonate agents.

Among the 65,011 patients, 16% of the patients used anti-osteoporosis medications during the first 12 months after hip fracture. This prevalence increased from 12 to 20% between 2010 and 2012, after which it stagnated (Fig. 2). Stratification on sex, age groups, comorbidity, and previous fracture within 10 years before index date showed a similar pattern (Fig. 3). Among the 6131 patients with 12-month pre-fracture use of anti-osteoporosis medications, 5516 were continuous users in the 12 months following the hip fracture. The prevalence of continuous use was stable between 2005 and 2012, whereupon it decreased between 2012 and 2014 (Fig. 2).

Among the 58,800 pre-fracture non-users, the 12-month cumulative incidence of post-fracture bisphosphonate initiation, with death as competing risk, was 17%. The cumulative incidence varied between 13 and 21% during the study period and was the highest among patients sustaining hip fracture in 2012 and the lowest among patients sustaining hip fracture in 2010. The 12-month cumulative incidence of a post-fracture

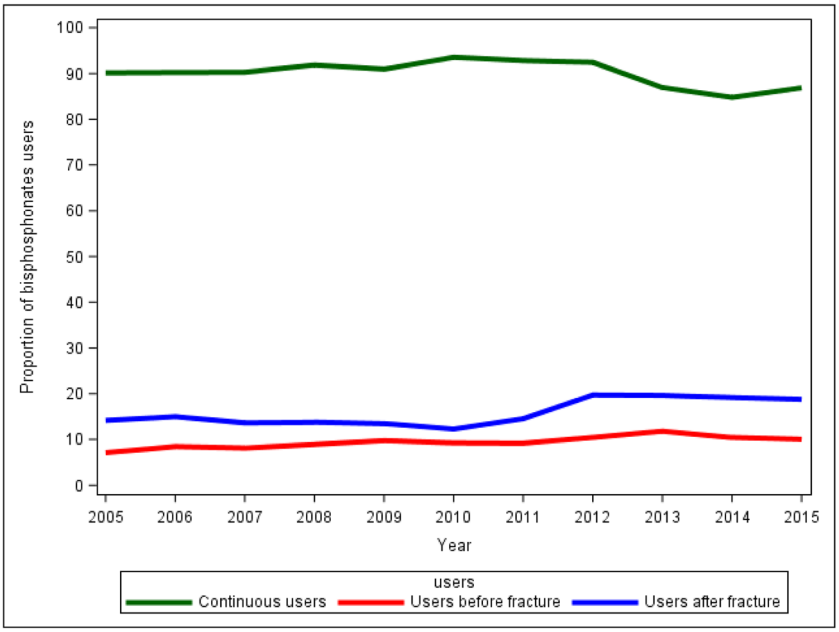


**Fig. 2** Prevalence of bisphosphonate users among hip fracture patients in Denmark, 2005–2015

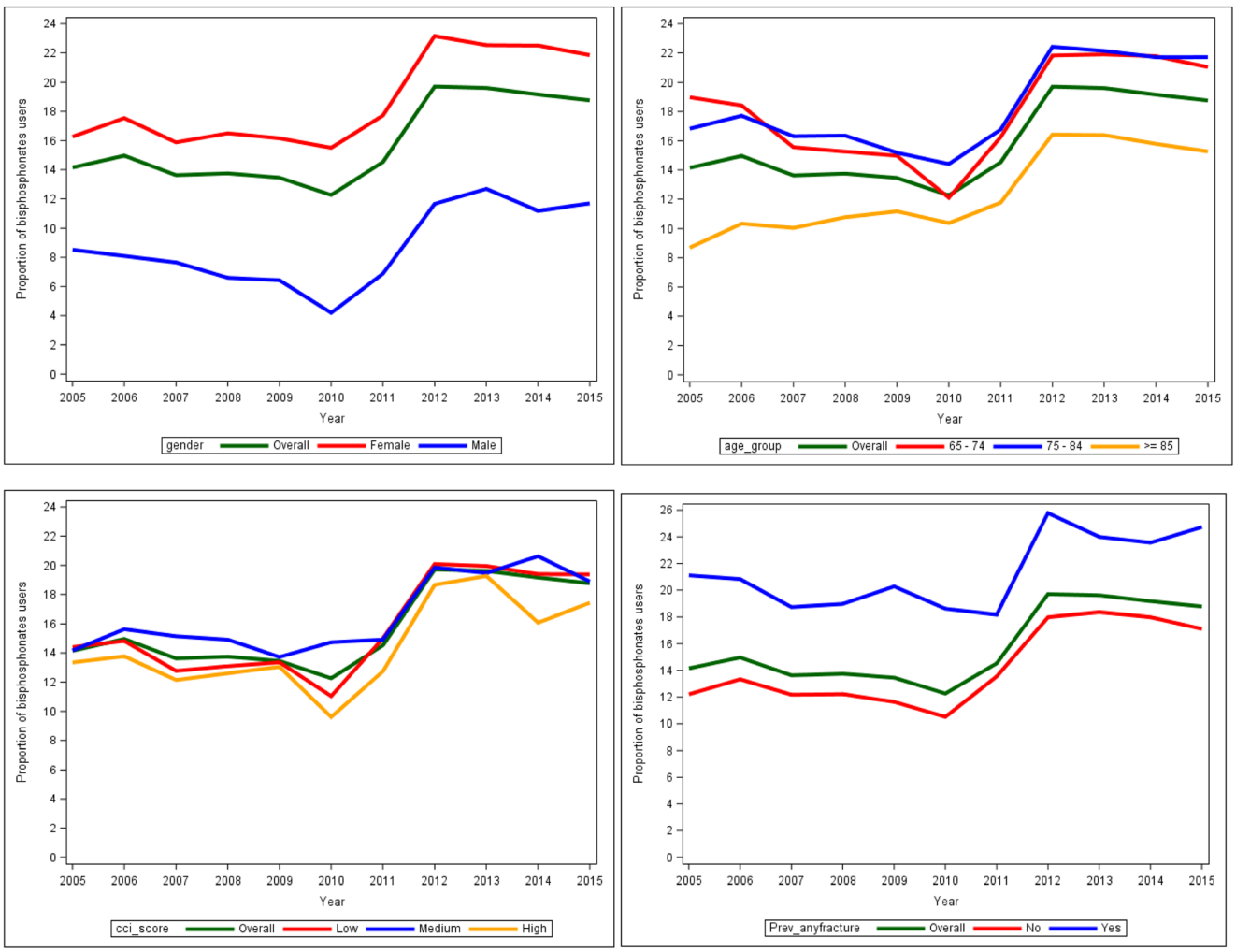


**Fig. 3** Prevalence of bisphosphonate use after hip fracture during 2005–2015 stratified for sex, age groups, comorbidity, and previous fracture ($N$ = 65,011)

bisphosphonate initiation was greater among women than among men, especially for patients 75 to 85 years old (Fig. 4), whereas the differences among patients with different comorbidities were minor. The cumulative incidence of a post-fracture bisphosphonate initiation was greater among patients with a previous fracture, but the development over time was the same (Fig. 4).

## Discussion

In this nationwide population-based cohort study with complete individual-level outpatient dispensing data, less than one-third of patients with hip fracture used anti-osteoporosis medication in the 12 months following the hip fracture. During the period 2005–2015, the proportion of bisphosphonate users following hip fracture increased only slightly, irrespective of sex, age, comorbidity level, or previous fracture.

The modest increase in use of bisphosphonates after hip fracture in Denmark is worrisome as it is recommended in international guidelines [30, 31] including the NICE Health Technology Appraisal No. 87 that women at age 75 or above with a hip fracture should be prescribed anti-osteoporosis medication without the need of prior dual-energy X-ray absorptiometry [16]. There may be clinical relevant reasons for not prescribing anti-osteoporotic medication after hip fracture including terminal cancer, renal impairment below 35 mL/L, or short life expectancy, but it is estimated that up to 70% of the hip fracture patients in Denmark may benefit from anti-osteoporotic medication [23]. In addition, a recent US study found that the initiation of anti-osteoporosis medication after hip fracture was associated with a meaningful reduction in subsequent non-vertebral fracture rates suggesting that improving anti-osteoporosis medication dispensing may result in notable public health benefits [7]. Following national guidelines for in-hospital hip fracture patient care, about 90% of hip fracture patients are discharged after the evaluation of need for medical osteoporosis prophylaxis has been performed [32]. The evaluation of need for medical osteoporosis prophylaxis is a process performance measure, which is

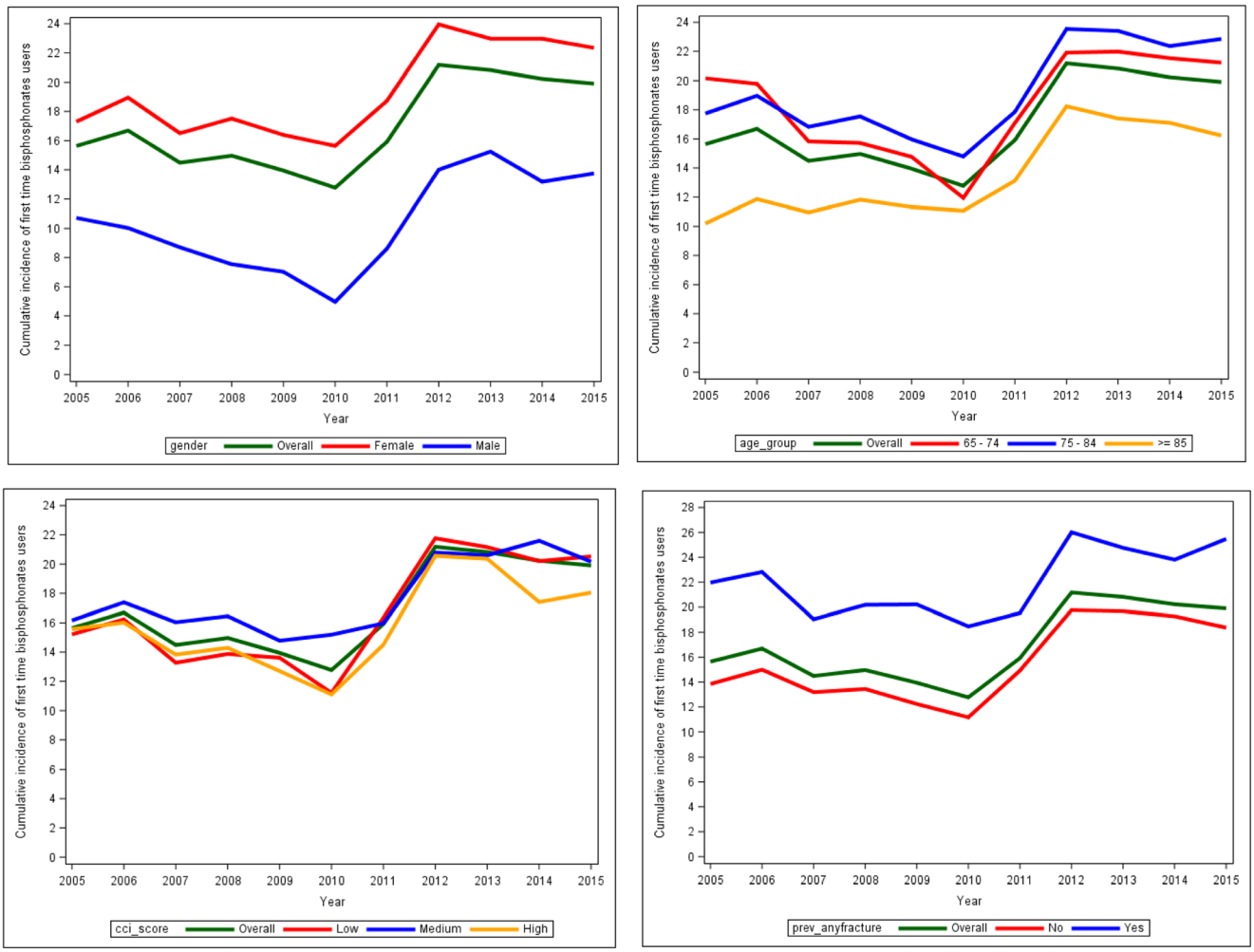


**Fig. 4** The cumulative incidence of first prescription of bisphosphonates within 1 year after hip fracture surgery, considering death as competing risk stratified according to sex, age groups, comorbidity, and previous fracture ($N = 65{,}011$)

fulfilled if the patient continues anti-osteoporosis medication, if the patient is referred to a DEXA scan, or if there is no indication for osteoporosis prophylaxis because the patient has cancer or a psychiatric condition. Waiting time for a DEXA scan is approximately 8 weeks. It is therefore surprising that only one-third of potentially treatment-eligible patients are on anti-osteoporosis medication 12 months after hip fracture. Also, the stagnation of incident users after hip fracture in the last years is worrisome. In Denmark, there are no standard guidelines for post-discharge clinical follow-up of hip fracture patients, i.e., patients do not receive follow-up appointment in outpatient clinics or at the general practitioners. Instead, patients are advised to see their general practitioners as needed. Since osteoporosis is often asymptomatic [31], patients may not seek contact with their general practitioner for osteoporosis. It is further debated who has the responsibility to follow up on secondary prevention: the patient, the primary sector, or the municipality, where rehabilitation of patients is carried out. Thus, better communication and transfer of patients from hospital to primary sectors and municipality could potentially improve secondary fracture prevention.

Similar to previous findings, we document lower than expected use of anti-osteoporosis medication after hip fracture according to the guidelines, particularly among men [14, 18, 33]. From 1995 to 2004 in the USA, the annual proportion of patients initiating osteoporosis medication, especially bisphosphonates, after hip fracture increased from below 5 to 22% [14]. However, newer studies from the USA have reported a decreasing use in the range of 13 to 21% in 2012 [11, 33] and a continuous decline to 3.3% in 2015 [7], presumably related to fears about potential adverse events from bisphosphonates or denosumab, such as osteonecrosis of the jaw, atypical femoral fractures, and atrial fibrillation, which have garnered attention in the media [34]. However, the adverse events are extremely rare, and the benefits of osteoporosis treatment in post-fracture patients outweigh the potential risks [35]. In the UK, the annual proportion of women with hip fracture prescribed anti-osteoporosis medication post-hip fracture increased from 8% in 2000 to 51% in 2010 [18, 36]. The pronounced trend in the UK compared with the low use and the lack of increase of bisphosphonate use in Denmark observed in this study may be related to the implementation of the Fracture Liaison Service and NICE guidelines. The Fracture Liaison Service does follow-up osteoporosis assessment after discharge, which may have bridged this gap between orthopedic departments and the general practitioners [37]. In addition, the NICE Health Technology Appraisal 87 from 2005 advocated for the use of anti-osteoporosis medication after hip fracture for women at age 75 years or older, even without requiring a prior dual-energy X-ray absorptiometry [16, 23].

The proportion of continuous users of bisphosphonates decreased after 2012. Denosumab was introduced to the Danish market in 2010 [38–40], and some patients, especially those with impaired kidney function [14], may have switched during hospital stay or in ambulatory after DEXA scan. This denosumab treatment would therefore not be captured by outpatient dispensing and thus may be related to the minor drop in continuous users after 2012.

Since women and elderly patients have a higher risk of fracture and re-fracture, we expected to see a higher increase over the years in the use of anti-osteoporosis medication among hip fracture patients who were female or elderly [41]. Furthermore, we expected a lower use of bisphosphonates among high-comorbidity patients due to a presence of contraindications. However, the use was nearly the same, irrespective of the sex, age, and comorbidity of the patient. The variation in the use of anti-osteoporosis medication was unrelated to differences in the observed patient characteristics, but may be related to health care organization, which remains to be elicited in future studies [42].

## Limitations

Anti-osteoporosis medication dispensing may not correspond to the actual intake of medication. However, studies have indicated a good correlation between self-reported medication use or general practitioner-reported medication use and prescriptions filled at pharmacies [43–45]. Furthermore, we did not have information on medications dispensed during hospitalization; thus, we may have underestimated the use and initiation of anti-osteoporosis medication. Especially the use of denosumab and zoledronate administered parenterally in an ambulatory is underestimated. However, in 2015, the overall use including both hospital and outpatient dispensing of zoledronate among persons 65 years or older accounted for less than 1% of the total use of anti-osteoporosis medication, while denosumab accounted for 20% in 2015, including among cancer patients (public access through www.medstat.dk, accessed December 2018).

## Perspective

Our findings have potential implications for clinical practice, future research, and policymakers. A low number of both incident and prevalent users of anti-osteoporosis medication following hip fracture is worrisome due to the high risk of re-fracture. Repeated fractures have serious consequences for the patients and society including further functional decline, reduced quality of life, mortality, and increasing health care costs. Due to an increase in life expectancy, hospitals may be facing an increasing number of hip fractures and, subsequently, re-fractures, unless patients are treated with anti-osteoporotic medication. Our results are also relevant for the policymakers, as the health care systems for years have failed to intervene on an evidence-based and cost-effective treatment

among patients with hip fracture. Our stratified analyses suggest that the use of anti-osteoporosis medication following hip fracture is not related to patient characteristics, but rather is related to health care organization. Results from the UK suggest that it seems possible to increase the use of anti-osteoporosis medication among hip fracture patients due to the standardization of the clinical follow-up course.

## Conclusions

This study provides evidence for a treatment gap in the use of anti-osteoporosis medication after hip fracture, as less than one-third of patients used an anti-osteoporosis medication within 12 months of surgery, regardless of sex, age, or comorbidity burden. The use of anti-osteoporosis medication increased by only 6 percent points following hip fracture during 2005–2015, irrespective of sex, age, or comorbidity level.

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**Authors' contributions** PKK and ABP conceived and designed the study. PKK, NS, VE, and ABP analyzed and interpreted the data. PKK drafted the manuscript. PKK, NS, VE, and ABP critically revised the manuscript for important intellectual content. All authors have given the final approval of the version to be submitted.

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**Compliance with ethical standards** The study was approved by the Danish Data Protection Agency (Aarhus University record number 2016-051-000001).

**Conflicts of interest** None.

## References

1. Kanis JA, Johnell O, Oden A, de Laet C, Oglesby A, Jönsson B (2002) Intervention thresholds for osteoporosis. Bone 31:26–31
2. Johnell O, Kanis JA (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 17:1726–1733
3. van Geel TA, van Helden S, Geusens PP et al (2009) Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis 68:99–102
4. von Friesendorff M, Besjakov J, Akesson K (2008) Long-term survival and fracture risk after hip fracture: a 22-year follow-up in women. J Bone Miner Res Off J Am Soc Bone Miner Res 23:1832–1841
5. Warriner AH, Patkar NM, Yun H, Delzell E (2011) Minor, major, low-trauma, and high-trauma fractures: what are the subsequent fracture risks and how do they vary? Curr Osteoporos Rep 9:122–128
6. Lyles KW, Colon-Emeric CS, Magaziner JS et al (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357:1799–1809
7. Desai RJ, Mahesri M, Abdia Y et al (2018) Association of osteoporosis medication use after hip fracture with prevention of subsequent nonvertebral fractures: an instrumental variable analysis. JAMA Netw Open 1:e180826
8. Elliot-Gibson V, Bogoch ER, Jamal SA et al (2004) Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: a systematic review. Osteoporos Int 15:767–778
9. Formiga F, Rivera A, Nolla JM, Coscujuela A, Sole A, Pujol R (2005) Failure to treat osteoporosis and the risk of subsequent fractures in elderly patients with previous hip fracture: a five-year retrospective study. Aging Clin Exp Res 17:96–99
10. Giangregorio L, Papaioannou A, Cranney A, Zytaruk N, Adachi JD (2006) Fragility fractures and the osteoporosis care gap: an international phenomenon. Semin Arthritis Rheum 35:293–305
11. Kim SC, Kim MS, Sanfelix-Gimeno G et al (2015) Use of osteoporosis medications after hospitalization for hip fracture: a cross-national study. Am J Med 128:519–26.e1
12. Rabenda V, Vanoverloop J, Fabri V, Mertens R, Sumkay F, Vannecke C, Deswaef A, Verpooten GA, Reginster JY (2008) Low incidence of anti-osteoporosis treatment after hip fracture. J Bone Joint Surg Am 90:2142–2148
13. Solomon DH, Morris C, Cheng H, Cabral D, Katz JN, Finkelstein JS, Avorn J (2005) Medication use patterns for osteoporosis: an assessment of guidelines, treatment rates, and quality improvement interventions. Mayo Clin Proc 80:194–202
14. Cadarette SM, Katz JN, Brookhart MA et al (2008) Trends in drug prescribing for osteoporosis after hip fracture, 1995-2004. J Rheumatol 35:319–326
15. Jennings LA, Auerbach AD, Maselli J, Pekow PS, Lindenauer PK, Lee SJ (2010) Missed opportunities for osteoporosis treatment in patients hospitalized for hip fracture. J Am Geriatr Soc 58:650–657
16. NICE (2008) Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women Technology Appraisal guidance [TA161]. London, National Institute for Health and Care Excellence
17. Khosla S, Hofbauer LC (2018) Osteoporosis: a roadmap to close the treatment gap. Lancet Diabetes Endocrinol 6:833
18. Klop C, Gibson-Smith D, Elders PJ et al (2015) Anti-osteoporosis drug prescribing after hip fracture in the UK: 2000-2010. Osteoporos Int 26:1919–1928
19. Shah A, Prieto-Alhambra D, Hawley S et al (2017) Geographic variation in secondary fracture prevention after a hip fracture during 1999-2013: a UK study. Osteoporos Int 28:169–178
20. och Socialstyrelsen S (2012) Öppna Jämförelser av hälso-och sjukvårdens kvalitet och effektivitet
21. Cauley JA, Chalhoub D, Kassem AM et al (2014) Geographic and ethnic disparities in osteoporotic fractures. Nat Rev Endocrinol 10:338–351
22. Rosengren BE, Bjork J, Cooper C et al (2017) Recent hip fracture trends in Sweden and Denmark with age-period-cohort effects. Osteoporos Int 28:139–149
23. Ryg J (2009) The Frail Hip. A study on the risk of second hip fracture, prevalence of osteoporosis and adherence to treatment in patients with recent hip fracture. Odense, Syddansk Universitet. Det Sundhedsvidenskabelige Fakultet
24. Lunde A, Tell GS, Pedersen AB et al (2019) The role of comorbidity on mortality after hip fracture: a nationwide Norwegian study of 38,126 women with hip fracture matched to a general population comparison cohort. Am J Epidemiol 188(2):398–407
25. Pedersen AB, Ehrenstein V, Szepligeti SK et al (2017) Thirty-five-year trends in first-time hospitalization for hip fracture, 1-year

mortality, and the prognostic impact of comorbidity: a Danish nationwide cohort study, 1980-2014. Epidemiology 28:898–905
26. Mainz J, Krog BR, Bjornshave B et al (2004) Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. Int J Qual Health Care 16(Suppl 1): i45–i50
27. Schmidt M, Pedersen L, Sorensen HT (2014) The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 29:541–549
28. Schmidt M, Schmidt SA, Sandegaard JL et al (2015) The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 7:449–490
29. Johannesdottir SA, Horvath-Puho E, Ehrenstein V et al (2012) Existing data sources for clinical epidemiology: the Danish National Database of Reimbursed Prescriptions. Clin Epidemiol 4:303–313
30. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R, National Osteoporosis Foundation (2014) Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25:2359–2381
31. Compston JE, McClung MR, Leslie WD (2019) Osteoporosis. Lancet 393:364–376
32. Regionernes Kliniske Kvalitets Program (2015) De kliniske kvalitetsdatabaser. Aarhus, Regionernes Kliniske Kvalitets Program
33. Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD (2014) Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. J Bone Miner Res 29:1929–1937
34. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, al Dabagh R, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, el Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J, on behalf of the International Task Force on Osteonecrosis of the Jaw (2015) Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res Off J Am Soc Bone Miner Res 30:3–23
35. Suresh E, Pazianas M, Abrahamsen B (2014) Safety issues with bisphosphonate therapy for osteoporosis. Rheumatology (Oxford) 53:19–31
36. Hawley S, Leal J, Delmestri A et al (2016) Anti-osteoporosis medication prescriptions and incidence of subsequent fracture among primary hip fracture patients in England and Wales: an interrupted time-series analysis. J Bone Miner Res 31:2008–2015
37. de Bruin IJA, Wyers CE, van den Bergh JPW, Geusens PPMM (2017) Fracture liaison services: do they reduce fracture rates? Ther Adv Musculoskelet Dis 9:157–164
38. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C, FREEDOM Trial (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361:756–765
39. Freemantle N, Satram-Hoang S, Tang ET et al (2012) Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int 23:317–326
40. Jonsson B, Strom O, Eisman JA et al (2011) Cost-effectiveness of denosumab for the treatment of postmenopausal osteoporosis. Osteoporos Int 22:967–982
41. Cauley JA (2017) Osteoporosis: fracture epidemiology update 2016. Curr Opin Rheumatol 29:150–156
42. Wennberg J, McPherson K, Goodman D Small area analysis and the challenge of practice variation. Medical practice variations, vol 2015. Springer, pp 1–25
43. Johannesdottir SA, Maegbaek ML, Hansen JG et al (2012) Correspondence between general practitioner-reported medication use and timing of prescription dispensation. Clin Epidemiol 4:13–18
44. Lokkegaard EL, Johnsen SP, Heitmann BL et al (2004) The validity of self-reported use of hormone replacement therapy among Danish nurses. Acta Obstet Gynecol Scand 83:476–481
45. Schneeweiss S, Avorn J (2005) A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 58:323–337

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