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ORIGINAL ARTICLE

Prescription of anti-osteoporosis medications after hospitalization for hip fracture: a multicentre Italian survey

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Abstract
Purpose Literature data indicate that the proportion of patients with recent hip fracture who receive a prescription for anti-osteoporotic drugs is low and does not seem to increase over time. This study aimed to obtain data on the prescription for anti-osteoporotic drugs in Italian patients discharged after a recent hip fracture and to assess which variables could have influenced the decision for prescribing osteoporosis medication.
Methods A total of four Italian centres located in four different geographical areas (Siena, Verona, Naples and Palermo) participated in this retrospective study. In each centre, experienced clinicians gathered the data of up to 200 consecutive patients discharged after a recent low-trauma hip fracture. The analysis was carried out on 697 patients (540 women and 157 men; mean age 81.9 ± 8.6 years).
Results The percentage of patients who were receiving any type of treatment for osteoporosis before the hip fracture was 8.8% (ranging from 2.4% in Naples to 17.4% in Verona). After the index hip fracture, only 23.2% of patients (namely 10.5% of men and 27.2% of women) received prescription for any pharmacological treatments for osteoporosis. Both female gender and previous use of medications for osteoporosis were positively associated with the likelihood of receiving prescription for anti-osteoporotic treatment at discharge.
Conclusions This study showed that less than 25% of the elderly Italian patients discharged after a hip fracture received a prescription for any type of treatment for osteoporosis and highlights the urgent need for implementing new strategies in the management of hip fracture patients.

Keywords Hip fracture · Anti-osteoporotic drugs · Comorbidities · Ca/vitamin D supplements

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Introduction

Osteoporosis is a major medical problem which has a remarkable financial impact on society. Hip fracture is considered the most serious complication of osteoporosis because of the disability, morbidity, mortality and cost to which it contributes [1, 2]. The bulk of non-traumatic hip fractures is due to both osteoporosis-related bone loss and age-related deterioration of bone quality [3]. In Italy, 90,000 hip fractures per year are reported in subjects aged 50 years or over with a growing trend [4]. Patients who suffer their first hip fracture are at greater risk of recurrent vertebral and non-vertebral osteoporotic fractures. In particular, in these patients the risk of a second hip fracture is as much as six times greater and with the risk of a non-hip fracture being nine to fifteen times greater, with 10% having another hip fracture within one year [5, 6]. At present, there is a growing conviction that focusing attention on patients with hip fractures may be of crucial

importance in reducing the burden of osteoporosis and subsequent fragility fractures [7–9]. Therefore, current national and international guidelines recommend the use of pharmacological treatments after hip fracture [10, 11]. Moreover, the results of several studies showed a decreased mortality rate in patients who were managed with anti-osteoporotic drugs as compared with those who were not [12–14]. In particular, in the HORIZON study [13] hip fracture patients were randomly assigned to receive annually zoledronic acid either by intravenous infusion or a placebo infusion; both groups received both oral calcium and vitamin D daily. In this latter study, the median follow-up was 1.9 years and in the zoledronic acid group there was a relative risk reduction of 28% for death from any causes [13]. Notwithstanding, many studies have reported that a significant proportion of hip fracture patients do not receive any treatment for osteoporosis. In fact, literature data indicate that the proportion of patients with recent hip fracture who receive a prescription of anti-osteoporotic drugs varies between 15 and 40% and does not seem to increase over time in any Western countries [15]. On the contrary, in more recent years the use of bisphosphonates, the most commonly used group of anti-osteoporotic drugs after hip fracture, decreased significantly over the years in both the USA and some European countries [15]. At present, in Italy very few data are available on the percentage of patients with recent hip fracture who are receiving prescriptions for anti-osteoporotic drugs. The aim of this study was twofold: (1) to obtain data on the prescription for anti-osteoporotic drugs in patients discharged after a recent hip fracture and (2) to assess which variables (comorbidities, age, etc.) could have influenced the decision for prescribing osteoporosis medication.

Materials and methods

A total of four Italian centres (Departments of Orthopedics and Rehabilitation) located in academic and non-academic general hospitals over four different geographical areas (Siena, Verona, Naples and Palermo) were invited to participate in this study. In each centre, experienced clinicians gathered the data of up to 200 consecutive patients, aged 65 years or over, discharged from 1 January 2014 to 31 December 2014 after a recent low-trauma hip fracture. Low trauma fractures were either spontaneous or caused by minimal trauma (trauma equal to or less than a fall from a standing position). The pathological hip fractures due to primary or metastatic bone cancer, multiple myeloma, Paget's disease of bone or primary hyperparathyroidism were excluded. The clinicians of each centre, by reviewing the clinical documents of patients, collected demographic data and information concerning the type of hip fracture, the type of surgical management of hip fracture, smoking habits and history of previous fragility fractures. The history of previous fragility fractures was ascertained both by self reporting (patient and/or caregiver) and, when available, from the assessment of health documentation. At each centre, hip fractures were classified on the basis of preoperative radiographs and surgical reports as cervical (or medial or intra-capsular) and trochanteric fractures (or lateral or extra-capsular). By reviewing clinical documents, information was also collected concerning the more frequent comorbidities and the use of medications known to interfere with bone metabolism such as glucocorticoids, diuretics, insulin and oral antidiabetic drugs, anticoagulants, proton pump inhibitors, antihypertensives and antidepressants. Detailed information on osteoporosis medications, either anti-osteoporotic drugs or calcium/vitamin D supplementation, taken in the 12 months before the index hip fracture, was also gathered. Concerning osteoporosis medications after index hip fracture, the clinicians of each centre considered not only those prescribed at discharge from orthopaedic wards but also those prescribed during the following rehabilitation period by other physicians. When necessary the clinical document information was confirmed by telephone to patients/caregivers and GPs. Study protocol was prepared according to the Declaration of Helsinki and subsequent integrations and was approved by the local ethical committee of each centre.

Statistical analysis

Continuous variables normally distributed were reported as the mean and standard deviation, while those not normally distributed were reported as the median and interquartile range. Categorical variables were reported as proportions and percentages. Statistical comparisons across groups were carried out by Chi-square test or Fisher's exact test as appropriate. Conditional logistic regression analysis was used in order to evaluate any possible associations between study variables and the prescription of osteoporosis medications. All statistical analyses were carried out by using statistical software (SPSS 10.1).

Results

Overall, the four participating centres enrolled 731 patients, but 34 were discarded for incomplete information on clinical data and pharmacological treatment. Therefore, the analysis was carried out on the remaining 697 patients. The distribution of demographic and clinical characteristics of the 697 hip fracture patients is shown in Table 1. The mean age of study population was high (81.9 ± 8.6 years)

Table 1 Distribution of demographic and clinical characteristics of 697 elderly patients with hip fractures

	All patients	Siena	Palermo	Verona	Naples
Number (male/female)	697 (540/157)	249 (187/62)	100 (80/20)	143 (111/32)	205 (162/43)
Age (years)	81.3 ± 8.6	83.6 ± 7.8	81.4 ± 8.8	83.7 ± 8.6	78.9 ± 8.4
Weight (kg)	65.1 ± 11.9	63.0 ± 13.5	62.5 ± 12.1	67.0 ± 10.2	69.6 ± 10.8
Height (cm)	161.5 ± 8.2	161.3 ± 8.3	159.2 ± 7.1	163.2 ± 8.6	–
Age at menopause (years)	49.5 ± 4.9	42.7 ± 13.4	50.5 ± 4.2	49.2 ± 3.9	47.9 ± 7.9
Number of children	1.7 ± 1.0	1.9 ± 1.0	1.5 ± 1.0	1.8 ± 0.9	2.4 ± 0.5
Patient's history of fracture, n/total n (%)	187/697 (26.8)	59/243 (23.7)	13/100 (13)	87/143 (60.8)	28/205 (13.7)
Smoking, n/total n (%)	79/697 (11.3)	9/249 (3.6)	16/100 (16)	51/143 (35.7)	3/205 (1.5)

and as expected there was a predominance of females (77.5%) with respect to males (22.5%), so that the ratio between the two sexes was 3.4. No significant differences in clinical and demographic parameters were observed among the four groups. Concerning the management of hip fractures, 57.9% of hip fracture patients underwent osteosynthesis procedure, whereas 32.2% underwent a prosthetic replacement and the remaining 9.9% received a conservative treatment. The most prevalent hip fractures were cervical (43%). Overall, 28.7% of hip fracture patients had a history of previous fragility fracture with the hip being the most prevalent site (10.2% of patients).

Almost all patients presented comorbidities and were taking several medications. Table 2 shows the distribution of reported comorbidities and of medications taken at the moment of the hip fracture both altogether and grouped by the participating centres. As expected, the more frequent comorbidities were: cardiovascular diseases (71.6%), dementia (38%), diabetes (23%), cancer (12.5%) and COPD (11.3%).

Figure 1 illustrates the distribution of patients by the use of drugs for osteoporosis before hip fracture and at discharge from orthopaedic wards or rehabilitation facilities. The patients were also stratified by the four participating centres. Overall, the percentage of patients who were receiving any type of treatment for osteoporosis before the hip fracture was 8.8% (ranging from 2.4% in Naples to 17.4% in Verona). No significant difference in the use of drugs for osteoporosis before hip fracture was found between the patients with or without a history of fragility fractures; moreover, only 6 of 56 (10.7%) with previous hip fracture were receiving anti-osteoporotic medications (data not shown). After the index hip fracture 23.2% of patients received prescription for pharmacological treatment for osteoporosis, whereas the remaining patients (76.8%) did not receive any prescriptions. Considering separately men and women, we found that 27.2% of women and 10.5% of men were prescribed for anti-osteoporotic treatments at discharge. Important differences were observed among the four participating centres. Strikingly, at the Siena centre the proportion of patients who received anti-osteoporosis medication was lower after than before the index hip fracture (9.1 vs 10.8%) (Fig. 1).

Moreover, the majority of hip fracture patients were only prescribed supplementation with calcium and/or vitamin D. Figure 2 shows the distribution of patients treated with the more common drugs for osteoporosis before and after the hip fracture. In particular, the prescription of bisphosphonates markedly increased while remaining low (4.7% after hip fracture vs 2.7% before). Moreover, the prescription of denosumab, practically non-existent before hip fracture, reached the 4% after hip fracture (Fig. 2). Only one patient was on treatment with teriparatide before hip fracture, and six patients were prescribed with teriparatide after the hip fracture (Fig. 2).

Logistic regression analysis showed that only female gender and previous use of anti-osteoporosis medications were positively associated with the likelihood of receiving prescription for anti-osteoporotic treatment at discharge (Table 3). Instead, the prescription of anti-osteoporotic treatments was seen not to be influenced by either age or previous fractures.

Discussion

This study provides relevant information on the current management of elderly Italian patients with a recent hip fracture. In particular, this study showed that less than 10% of the elderly Italian patients discharged after a hip fracture were receiving treatments for osteoporosis before the fracture. Even more significant is the finding that more than 75% of patients were discharged without receiving prescription for any pharmacological treatment for osteoporosis and less than 10% received prescription for teriparatide or anticatabolic drugs (i.e. denosumab and bisphosphonates).

Our results seem to be in agreement with most of the relevant studies which reported that the rate of treatment with anti-osteoporosis drugs is very low, ranging from 5 to 50%.

Table 2 Distribution of clinical characteristics of 697 elderly patients with hip fractures

Characteristics	All patients	Siena	Palermo	Verona	Naples
Comorbidities	672/697 (96.4)	243/249 (97.6)	97/100 (97.0)	140/143 (97.9)	192/205 (94.1)
Heart failure, n/total n (%)	499/697 (71.6)	144/249 (57.8)	87/100 (87.0)	106/143 (74.1)	162/205 (79.0)
Depression, n/total n (%)	73/697 (10.5)	31/249 (12.4)	5/100 (5.0)	19/143 (13.3)	18/205 (8.8)
Dementia, n/total n (%)	111/697 (38.0)	45/249 (18.1)	12/100 (12.0)	23/143 (16.1)	31/205 (15.1)
Diabetes, n/total n (%)	160/697 (23.0)	39/249 (14.9)	30/100 (30.0)	32/143 (22.4)	59/205 (28.8)
COPD, n/total n (%)	79/697 (11.3)	30/249 (12.0)	6/100 (6.0)	15/143 (10.5)	28/205 (13.7)
Chronic kidney disease, n/total n (%)	49/697 (7.0)	17/249 (6.8)	7/100 (7.0)	12/143 (8.4)	13/205 (6.3)
Rheumatoid arthritis, n/total n (%)	9/697 (1.3)	3/249 (1.2)	1/100 (1.0)	1/143 (0.7)	4/205 (2.0)
Breast cancer, n/total n (%)	17/697 (2.4)	10/249 (4.0)	2/100 (2.0)	1/143 (0.7)	5/205 (2.4)
Prostate cancer, n/total n (%)	13/697 (1.9)	9/249 (3.6)	1/100 (1.0)	1/143 (0.7)	2/205 (1.0)
Other cancers, n/total n (%)	57/697 (8.2)	25/249 (10.0)	5/100 (5.0)	10/143 (7.0)	7/205 (3.4)
Liver diseases, n/total n (%)	35/697 (5.0)	5/249 (5.0)	3/100 (3.0)	10/143 (7.0)	17/205 (8.3)
Inflammatory bowel disease, n/total n (%)	3/697 (0.4)	2/249 (0.8)			1/205 (0.5)
Hyperthyroidism, n/total n (%)	11/697 (1.6)	4/249 (1.6)		7/143 (4.9)	
Hypothyroidism, n/total n (%)	62/697 (8.9)	24/249 (9.6)	13/100 (13.0)	12/143 (8.4)	13/205 (6.3)
Parkinson's disease, n/total n (%)	28/697 (4.0)	12/249 (4.8)	3/100 (3.0)	5/143 (3.5)	8/205 (3.9)
Kidney stones, n/total n (%)	11/697 (1.6)	3/249 (1.2)	3/100 (3.0)	3/143 (2.1)	2/205 (1.0)
Medications	672/697 (96.4)	249/249 (100.0)	100/100 (100.0)	139/143 (97.2)	184/205 (89.8)
Antihypertensives, n/total n (%)	444/697 (63.7)	134/249 (53.8)	80/100 (80.0)	78/143 (54.5)	152/205 (74.1)
Diuretics, n/total n (%)	230/697 (33.0)	114/249 (45.8)	7/100 (7.0)	53/143 (37.1)	56/205 (27.3)
Antidepressants, n/total n (%)	80/697 (11.5)	33/249 (13.3)	6/100 (6.0)	22/143 (15.4)	19/205 (9.3)
Proton pump inhibitors, n/total n (%)	402/697 (57.7)	233/249 (93.6)		72/143 (50.3)	97/205 (47.3)
Glucocorticoids, n/total n (%)	22/697 (3.1)	17/249 (6.8)			5/205 (2.4)
Anticoagulants, n/total n (%)	30/697 (4.3)	1/249 (0.4)	1/100 (1.0)	15/143 (10.5)	13/205 (6.3)
Antiplatelets, n/total n (%)	232/697 (33.3)	96/249 (38.6)	32/100 (32.0)	45/143 (31.5)	59/205 (28.8)
Oral antidiabetic, n/total n (%)	100/697 (14.3)	26/249 (10.4)	15/100 (15.0)	25/143 (17.5)	34/205 (16.6)
Insulin, n/total n (%)	45/697 (6.5)	9/249 (3.6)	11/100 (11.0)	2/143 (1.4)	23/205 (11.2)
Antipsycotic, n/total n (%)	95/697 (13.6)	70/249 (28.1)	1/100 (1.0)	9/143 (6.3)	15/205 (7.3)

In particular, the percentage of hip fracture patients who received prescription for anti-osteoporosis drugs was 19% in the study by Gardner et al. [16] and 15% in the study by Panneman et al. [17]. A large study carried out in Belgian patients who had sustained hip fracture reported that only 6% received treatment [8]. Moreover, this latter study also reported that of the patients who were treated, only 41% were continuing with their treatment by the end of the first year, and fewer than half were found to be compliant [8]. A recent cross-national study by Kim et al. [15] reported that the use of osteoporosis medications after hospitalization for hip fracture ranged from 11% in the USA to 38% in Korea. This latter study also reported that in the USA the proportion of patients who received an osteoporosis medication was lower after the index hip fracture than before [15]. Moreover, several studies carried out in both the USA and Europe reported that over the past decade there was a significant decrease in the rate of osteoporosis medication after hip fracture, which may be related to concerns over potential side effects of bisphosphonates [15, 18]. The reasons for the gap between national and international evidence-based treatment guidelines [10, 19] and treatment rates remain unclear and have been debated in several studies [8, 20]. Concerns over potential side effects of bisphosphonates and other osteoporosis treatments play an important role. Other barriers could be the confusion regarding which physician is responsible for treating osteoporosis in hip fracture patients (orthopaedic surgeon? Internist/rheumatologist? Primary care physician?), a lack of awareness by patients and physicians regarding the treatment guidelines and the efficacy of medications for osteoporosis following hip fracture and the presence of comorbidities with resulting need for polypharmacy. In fact, hip fracture is associated with increase in drug use, as a result of a global deterioration of health conditions [21]. However, recent literature data suggest that the implementation of multidisciplinary integrated models of care for patients with fragility fracture (e.g. Fracture Liason Service) may optimize the identification of

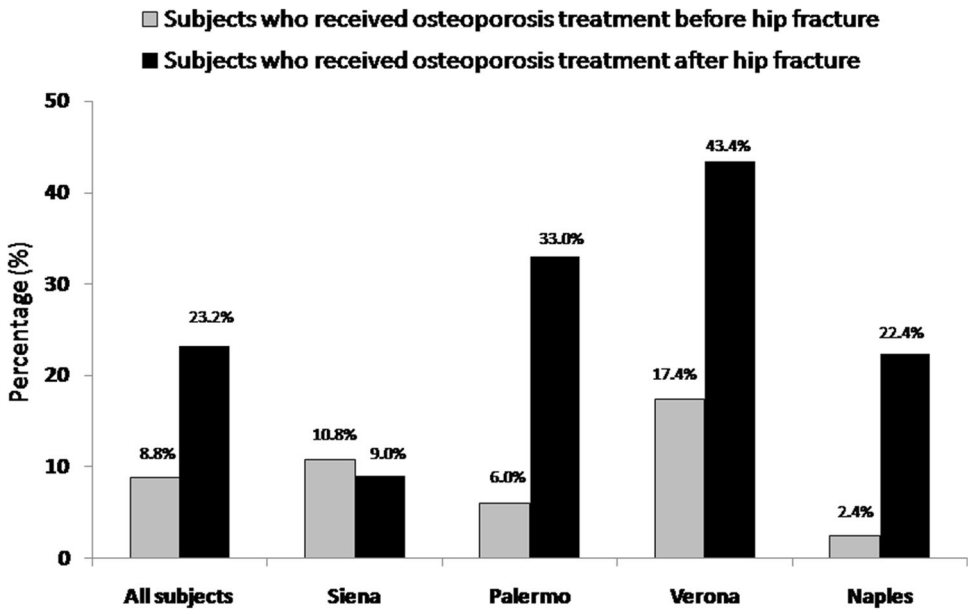

Fig. 1 Percentage of patients who received treatment for osteoporosis *before* and *after* the index hip fracture

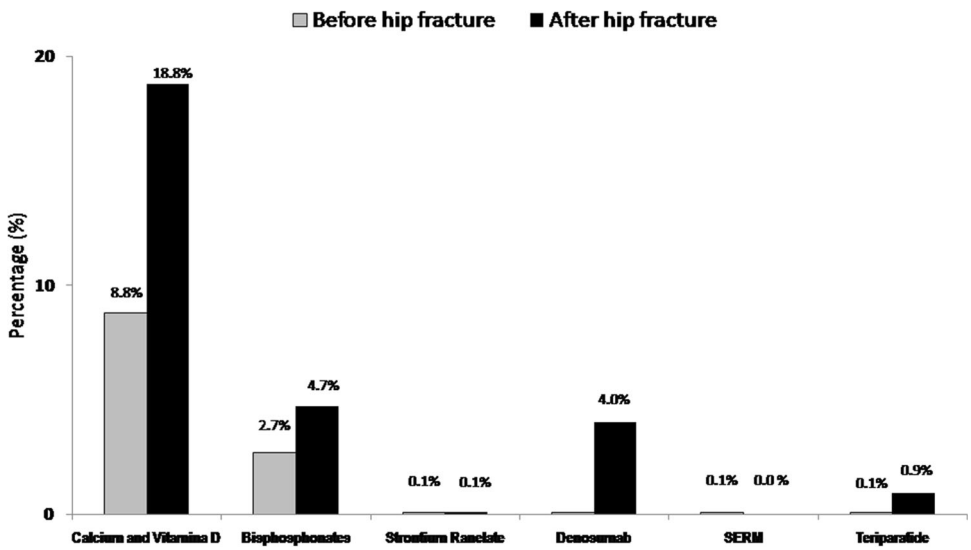

Fig. 2 Percentage of different anti-osteoporotic treatments *before* and *after* hip fracture

Table 3 Multiple logistic regression with regard to prescription for anti-osteoporotic treatment

	Odds ratio	95% CI	*p* value
Age	1.176	0.762–1.815	0.463
Previous fractures	0.650	0.407–1.039	0.071
Sex	2.606	1.406–4.829	0.002
Previous osteoporotic therapy	6.215	2.978–12.969	0.001

patients at highest risk and make possible an adequate pharmacological treatment in a larger number of patients [22, 23]. Moreover, a recent study by Giannini et al. [24] carried out in the Veneto region of Italy suggested that a more comprehensive approach to osteoporosis management might reduce hip fracture incidence in people aged 65 years or over.

This study has shown a marked variability in the use of osteoporosis medications across the four centres located in different Italian geographical areas which could be explained mainly by the different characteristics of the departments and by differences in management.

Another important point is to understand which characteristics of patients with hip fracture may influence the decision to prescribe drugs for osteoporosis. Previous data reported a higher proportion of comorbidities among BP users compared with patients untreated with anti-osteoporotic drugs [9]. In agreement with previous reports, our

study has evidenced that male patients have less possibility of receiving anti-osteoporotic treatments [25]. While a precise explanation for the discrepancy in treatment rates between women and men has not been identified, there is a well-recognized tendency by both medical professionals and patients to consider osteoporosis a disease of women. Also, the use of anti-osteoporosis drugs before the index hip fracture increased the likelihood of receiving anti-osteoporotic drugs at discharge. Moreover, in our study the presence of comorbidities and the drugs taken before the hip fracture did not seem to influence the prescription at discharge.

Our study has some limitations. Firstly, the observational, retrospective design does not allow the establishment of any causality relationships between the parameters. Secondly, this study was unable to assess whether osteoporosis medication prescribed was in reality taken by the patients. Thirdly, our results may have underestimated the use of osteoporosis medication; in fact, it is possible that some patients may have received a prescription for anti-osteoporotic drugs directly from their primary care physicians.

In conclusion, from our data it is evident that many patients, even after sustaining a hip fracture, do not receive anti-osteoporosis treatment, indicating that also in Italy severe osteoporosis often remains untreated or undertreated. Moreover, this study highlights the urgent need for implementing new strategies in the management of hip fracture patients in order to improve secondary prevention of fragility fractures.

Compliance with ethical standards

Conflict of interest Stefano Gonnelli, Carla Caffarelli, Giovanni Iolascon, Francesco Bertoldo, Giulia Letizia Mauro, Aurora Patti and Ranuccio Nuti declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration. Procedures performed in this study did not involve animals.

Informed consent For this type of study formal consent is not required.

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