Analysis of the costs and consequences of adherence to therapy in hip fracture patients. Results of a longitudinal analysis of *administrative databases*

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Summary

The aim of this study, a retrospective cohort analysis, was to calculate the costs and consequences of exposure to and compliance with drug treatments recommended for refracture prevention in post-menopausal women with hip fracture. All women aged ≥65 years and admitted to hospital with a main or secondary diagnosis of hip fracture in the period 1 January 2006 – 31 December 2008 were included. These patients were classified as *exposed*/*not exposed* to a drug treatment for fracture prevention. *Adherence* to treatment was calculated in the group of patients treated with bisphosphonates. The following items were considered in the cost analysis: drug treatments supplied, diagnostic tests administered and hospital admissions recorded during the observation period. In total, 5,167 patients were included in the analysis, of whom only 33.9% received drug therapy post hip fracture; of those treated with bisphosphonates, only 21.1% were found to have adhered to the treatment. Exposure to drug treatment reduced the risk of refracture by 39.5% and the risk of death by 55.1%. The mean cost increases observed in the patients who, according to indication, were exposed to drug treatment (+ € 256) or submitted to a diagnostic test (+ € 40) were offset by a sizeable reduction in costs of hospitalisation for refracture (- € 703). Drug treatment for the prevention of bone refractures in hip fracture patients was found to be *effective* in reducing the risk of refracture and death, and *cost-effective*, reducing overall patient management costs.

KEY WORDS: adherence to treatment, cost of disease, drug use, hip fracture, osteoporosis.

Introduction

Adherence to treatment, meaning the extent to which therapeutic indications are translated into clinical practice, is a key factor in the prevention of bone fractures (1,2). Many studies have indeed shown reduced compliance with treatment to be the main cause of failed pharmacological prevention associated with increased risk of refracture (3-8). With regard to bisphosphonates, the drug class most commonly used for the prevention of bone fractures associated with osteoporosis, adherence to treatment was unsatisfactory in between 35% and 65% of patients (9-13), leading to a 45% increase in fracture risk compared to recommendation compliant use of the drug therapy (3,6). From these findings it is thus clear that reduced adherence is a significant phenomenon from the epidemiological point of view and a factor that influences treatment.
In addition to its impact on the state of health of the population, inadequate prevention of bone fractures also contributes to inducing substantial avoidable costs (14-16). In Italy, the annual costs of hospitalisations and surgery for hip fractures are estimated to amount to almost half a billion euros (17), a figure in line with estimates in other western countries (18,19). In addition to these items, it is also necessary to consider rehabilitation which, again according to Italian estimates, generates a cost as great as that of hospitalisations and surgical operations (18). The size of this problem is further increased by the fact that, according to a survey recently carried out in Italy, the percentage of patients complying with bisphosphonate treatments, already rather low (19.6%), has actually fallen slightly over recent years (dropping from 20.4% in 2007 to 19.6% in 2008) (20).
The aim of this study was to calculate the costs and consequences of exposure to and compliance with drug treatments recommended for refracture prevention in post-menopausal women with hip fracture. Comparing the costs and consequences of drug treatments is a useful means of ascertaining the economic sustainability of bone refracture prevention strategies.

Methods

Data source
The data of the analysed subjects were drawn from the *administrative databases* of Local Health Units (LHUs) located in the North, centre and South of Italy and together covering a total of 2 millions healthcare system beneficieries. Each LHU, in order to monitor the healthcare services provided to its users, has information flows relating to *pharmaceutical care*, *outpatient services care* (eg, diagnostic tests and specialist visits), *hospital discharge records* and *deaths*. In each of these information flows, the services provided can be linked to the patient who received them. Through appropriate data linkage procedures, a population database including analytical and chronological data for all LHU's beneficieries can be created. These databases are called *administrative databases* and many previous studies have validated their use

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for the purpose of conducting drug use analyses (21-23). In compliance with privacy laws, the patients' identification code was encrypted and the individuals/bodies involved in processing the data for the purposes of the analysis were not given any data that might enable them to trace, directly or indirectly, any patient. In accordance with current regulations on the conducting of observational studies, the Ethics Committees of the participating LHUs were informed of this study.

Patients included
This retrospective cohort analysis included all women aged ≥65 years and admitted to hospital with a main or secondary diagnosis of hip fracture (ICD9 codes: 820, 821) in the period 1 January 2006 – 31 December 2008. The date of discharge from hospital was taken as the date of enrolment in the study. Patients hospitalised with a main or secondary diagnosis of bone cancer, bone metastases or pathological fracture (ICD9 codes: 170, 198.5, 733.1) were excluded from the analysis.

Drug treatments
The patients included in the analysis were classified as *exposed* or *not exposed* to a drug treatment for the prevention of bone fracture according, respectively, to the *presence* or *absence* of at least one prescription of bisphosphonates (ATC codes: M05BA e M05BB), strontium ranelate (codice ATC: M05BX03), parathyroid hormones and analogues (ATC code: H05AA), calcitonin preparations (ATC code: H05BA), raloxifene (ATC code: G03XC01), calcium (ATC code: A12AA), vitamin D (ATC code: A11CC), or combined calcium and vitamin D preparations (ATC code: A12AX) within the 12 months following their discharge from hospital (observation period). In the patients treated with bisphosphonates (whether or not they were receiving other treatments), *adherence* to treatment was calculated. The number of days covered in each prescription was calculated and added to the number of days covered in all the other prescriptions. The total number of days covered was related to the number of days in the observation period (365) and multiplied by 100. Patients in whom the total number of days covered amounted to more than 80% of the observation period were deemed compliant with the therapeutic recommendations.
During the observation period, the included patients were characterised on the basis of the presence of at least two prescriptions of the main concomitant drugs, such as corticosteroids, diuretics, enzyme inhibitors, antidiabetic agents, benzodiazepines, antidepressants, thiazide diuretics, beta-blockers, statins, non-steroidal anti-inflammatory drugs, analgesics and gastroprotective agents.
In the case of patients who, during the observation period, died or were transferred to other LHUs, the analysis of drug treatments was conducted until the date of death or transfer.

Diagnostic tests
The included patients were classified as *exposed*/*not exposed* to an instrumental or laboratory diagnostic test related to their bone fracture according to the presence/absence of at least one prescribed examination from among the following: X-ray, of the ribs, sternum, clavicle (codes 87.43.), cervical, thoracic (dorsal), lumbar (lumbosacral) spine (codes 87.2.), or shoulder, elbow, wrist, pelvis, hip, ankle, lower limbs, rotula (codes 88.2.), MRI scan with contrast of the cervical, thoracic, lumbosacral spine (code 88.93.1), total body X-ray bone densitometry (DEXA), CT bone density scan of the lumbar spine, ultrasound bone densitometry (codes 88.99.), measurement of total calcium (code 90.11.4), alkaline phosphatase (code 90.23.5), alkaline phosphatase isoenzyme (code 90.24.1), phosphorus (code 90.24.5).

Cost of healthcare services
The cost analysis was conducted taking into account all the healthcare services – drug treatments, diagnostic tests and hospital admissions – provided during the observation period or up to the date of the first relevant hospital admission (if sooner). Only admissions for a main or secondary diagnosis of fracture of the spine (code ICD9: 805; 806), hip (code ICD9: 820; 821), radius or ulna (code ICD9: 813.4; 813.5), humerus (code ICD9: 812.0-812.5), pelvis (code ICD9: 808), tibia or fibula (code ICD9: 823), ankle (code ICD9: 824) or ribs (codes ICD9: 807.0; 807.1) were considered relevant.
In the case of patients who died or were transferred to another LHA during the observation period, the cost analysis was conducted until the date of the death or transfer. In the patients in whom these events did not occur, the cost analysis was conducted until the end of the observation period.
The costs of drug treatments, diagnostic tests and hospitalisations were quantified on the basis of national and regional rates and DRG (Diagnosis-Related Group) rates.

Statistical analysis
The data are expressed as mean values ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Pearson's chi-square test and one-way ANOVA were used to test for differences in patient characteristics in relation to exposure to and adherence to treatment. The risk of any-cause death and of hospitalisation (fatal and non-fatal) with a main or secondary diagnosis of fracture was calculated using a Cox regression model in which hazard ratios were estimated in relation to adherence to the diagnostic-therapeutic recommendations. The other covariates included in the model were: the age of the patient, the presence of treatment with thiazide diuretics or related formulations, anti-inflammatory drugs, gastroprotective drugs, oral antidiabetics, or statins, the presence of a history of treatment for osteoporosis, the presence of a previous hospitalisation for hip fracture, the presence of a previous cardiovascular hospitalisation, and the presence of at least one spinal X-ray during the observation period. Patients sustaining a hip refracture within 45 days of the enrolment discharge from hospital were excluded from the regression model since these fractures may not, in fact, have been new fractures.
The level of statistical significance was set at $p<0.05$. All the analyses were conducted using SPSS for Windows (SPSS Inc., Chicago, Illinois), version 15.0.

Results

A total of 5,210 patients was selected for this study. Of these, 43 (0.9% of the selected patients) were excluded because they were admitted to hospital with a diagnosis of bone cancer, bone metastases or pathological fracture. The 5,167 patients included in the analysis had a mean age of 82.3±7.4 years (range, 65-103 years).
Exposure to drug treatment for bone fracture prevention was found in 33.9% of the included patients; of these, 26.9% had also received treatment prior to the hip fracture (Table 1). Exposure to drug treatment was found to be correlated with patient age. In particular, exposure to drug treatment decreased progressively with increasing age (45.5%, 37.0% and 25.7% at 65-74, 75-84 and >85 years of age, respectively) (Table 2). As regards the drug treatments prescribed at discharge, the monotherapies most commonly used were bisphosphonates (22.7% of patients), vitamin D (19.0%) and combined calcium and vitamin D preparation, (31.5%). Conversely, 17.9% of the patients received a combination therapy. The most frequent combination therapies were bisphosphonates and vitamin D (4.4%), and bisphosphonates together with combined calcium and vitamin D preparations (7.7%).
In the patients exposed to treatment with bisphosphonates, either in monotherapy or in a combination therapy (15.0% of the included patients), adherence to the treatment was found to be low, in-

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Table 1 - Exposure to fracture prevention drug treatment prior to and following hip fracture.

	n.	*%*
Never treated	3,185	61.6
Treated only prior to fracture	228	4.5
Treated only after fracture	1,283	24.8
Always treated	471	9.1
Total	**5,167**	**100.0**

Table 2 - Exposure to fracture prevention drug treatment by patient age.

Characteristics	*Not treated*	*Treated*	*Total*
Patients (n; %)	3,413	1,754	5,167
	66.1	33.9	100.0
65 - 74 years	440	367	807
	54.5	45.5	100.0
75 - 84 years	1,479	870	2,349
	63.0	37.0	100.0
85 years and over	1,494	517	2,011
	74.3	25.7	100.0

termediate and high in 42.8%, 36.1% and 21.1% of the cases, respectively (Figure 1). As with exposure to treatment, adherence to treatment was found to be inversely associated with increasing age of the patients.

In 47.6% of the included patients, at least one bone fracture-related instrumental diagnostic test was ordered (Table 3). In particular, at least one X-ray of the cervical, thoracic (dorsal), or lumbar (lumbosacral) spine was ordered in 5.9% of the patients, and at least one total body DEXA, CT bone density scan of the lumbar spine, or ultrasound bone densitometry in 2.1% of the patients.

In the patients receiving treatment with bisphosphonates, in monotherapy or in combination therapy regimens, the rate of ordering of at least one instrumental diagnostic test was found to vary in relation to exposure to the treatment but not in relation to the level of adherence. The patients submitted to at least two bone fracture-related instrumental diagnostic tests accounted for 25.4% of the patients included (Table 3).

Requests for at least one bone fracture-related laboratory diagnostic test were made in 21.9% of the included patients (Table 3).

The survival analysis revealed a total of 1,044 refracture-related events (deaths or hospitalisations). The incidence of combined events was found to be significantly reduced in the presence of drug therapy (-52.9%, $p<0.001$) and instrumental diagnostic testing (spine X-ray) (-54.9%, $p=0.001$). These results were also confirmed when analysing the single events: the incidence of death was significantly reduced in the presence of drug treatment (-55.1%, $p<0.001$) and of instrumental diagnostic testing (spine X-ray) (-58.6%, $p<0.01$); the incidence of hospitalisation for refracture, too, was reduced in the presence of drug treatment (-39.5%, $p<0.001$) and of instrumental diagnostic testing (spine X-ray) (-51.1%, $p<0.05$).

Cost of healthcare services

The total cost of bone fracture-related healthcare services provided to the included patients during the observation period was € 5,001,876, of which € 396,182 (7.9% of the total cost) was for drug treatments, € 250,943 (5.0%) for diagnostic tests, and € 4,354,750 (87.1%) for hospitalisations for refractures (Tables 4 and 5).

The mean cost of drug treatments increased from € 0.00 in the untreated patients to € 255.77 in the treated patients, while that of diagnostic testing ranged from € 36.66 (untreated patients) to € 76.37 (treated patients); conversely, the mean cost of hospitalisations for refracture fell from € 1,053.49 in the untreated to € 350.69 in the treated patients. Consequently, the average total cost fell from € 1,090.15 in the untreated to € 682.83 in the treated patients (Table 4).

In the patients exposed to treatment with bisphosphonates, the average cost for fracture prevention drugs was found to increase with increased adherence to treatment (€ 27.38 in the untreated patients, € 256.11 in the treated patients with low adherence, € 466.98 in the treated patients with intermediate adherence and € 603.96 in the treated patients with high adherence). A similar

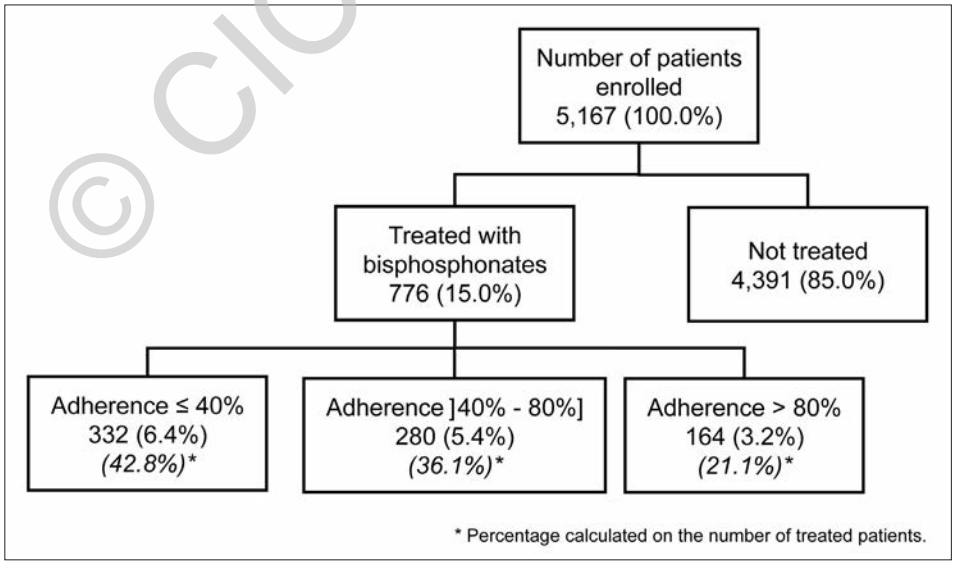

Figure 1 - Exposure and adherence to treatment with bisphosphonates in the period following hip fracture.

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Table 3 - Exposure to instrumental or laboratory tests in hip fracture patients.

	Not treated	Treated			Total
		Adherence ≤ 40%	Adherence]40% - 80%]	Adherence > 80%	
Instrumental diagnostic tests					
At least one request (n., %)	1,977	206	174	105	2,462
	45.0	62.0	62.1	64.0	47.6
At least two requests (n., %)	998	134	110	70	1,312
	22.7	40.4	39.3	42.7	25.4
Laboratory tests					
At least one request (n., %)	901	101	92	37	1,131
	20.5	30.4	32.9	22.6	21.9
At least two requests (n., %)	284	39	29	9	361
	6.5	11.7	10.4	5.5	7.0

Table 4 - Total cost of fracture-related healthcare services in relation to exposure to fracture prevention drug treatment.

		Drug treatments	Diagnostic tests	Hospitalisations for refracture	Total
Not treated	N. patients	3,618	3,618	3,618	3,618
	Mean cost (€)	0.00	36.66	1,053.49	1,090.15
	Total cost (€)	0.00	132,645.37	3,811,532.75	3,944,178.12
Treated	N. patients	1,549	1,549	1,549	1,549
	Mean cost (€)	255.77	76.37	350.69	682.83
	Total cost (€)	396,181.86	118,297.94	543,217.67	1,057,697.47
Total	N. patients	5,167	5,167	5,167	5,167
	Mean cost (€)	76.68	48.57	842.80	968.04
	Total cost (€)	396,181.86	250,943.31	4,354,750.42	5,001,875.59

pattern was found when analysing the average cost for diagnostic testing (€ 43.72 in the untreated patients, € 79.37 in the treated patients with low adherence, € 77.44 in the treated patients with intermediate adherence and € 88.97 in the treated patients with high adherence). Conversely, the average cost of hospitalisations for refractures fell with increasing adherence (€ 924.69 in the untreated patients, € 396.43 in the treated patients with low adherence, € 252.27 in the treated patients with intermediate adherence, and € 175.19 in the treated patients with high adherence). As a result, the average total cost for the first year of observation was sufficiently constant with increasing adherence (€ 995.80 in the untreated patients, € 731.91 in the treated patients with low adherence, € 796.69 in the treated patients with intermediate adherence and € 866,12 in the treated patients with high adherence) (Table 5).

Discussion

This study produced two main findings that support the existing evidence on refracture risk prevention in hip fracture patients. First, it confirmed the findings of several previous studies regarding the relationship between increased adherence to treatment and reduction of the risk of refracture or death (3-8). Second, it showed that greater adherence is *cost saving,* given that the increased drug treatment (and diagnostic testing) costs were well offset by the reduction in the costs of hospitalisations.

The relationship between adherence to treatment and risk of refracture or death was significant both generally (exposure to drug treatment reduced the risk of refracture or death by 52.9%) and when considering these two outcomes separately (exposure to drug treatment reduced the risk of death by 55.1% and of refracture by 39.5%). Analysis of parameters associated with the risk of refracture or death also highlighted the importance of diagnostic tests. In particular, having a spine X-ray was found to be associated with a reduced fracture risk (-51.1%) and a reduced risk of death (-58.6%). This finding could be attributable to patients taking greater care after receiving their X-ray results. Obviously, this interpretation, while plausible, is not verifiable, given the absence of test outcome values.

With regard to treatment exposure and adherence, this study confirmed that the values in clinical practice are particularly unsatisfactory (9-13,20). Only 33.9% of hip fracture patients were exposed to drug treatments; moreover, of those treated with bisphosphonates, only 21.1% used the drugs in accordance with the therapeutic indications that constitute a guarantee of the ef-

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Table 5 - Total cost of fracture-related healthcare services by adherence to treatment with bisphosphonates.

Levels of adherence to treatments with bisphosphonates		*Drug treatments*	*Diagnostic tests*	*Hospitalisations for refracture*	*Total*
Not treated with bisphosphonates	N. patients	4,491	4,491	4,491	4,491
	Mean cost (€)	27.38	43.72	924.69	995.80
	Total cost (€)	122,985.59	196,364.66	4,152,786.91	4,472,137.16
Treated, with adherence ≤ 40%	N. patients	295	295	295	295
	Mean cost (€)	256.11	79.37	396.43	731.91
	Total cost (€)	75,552.21	23,412.82	116,947.72	215,912.75
Treated, with adherence [40%-80%]	N. patients	237	237	237	237
	Mean cost (€)	466.98	77.44	252.27	796.69
	Total cost (€)	110,674.26	18,353.53	59,788.87	188,816.66
Treated, with adherence > 80%	N. patients	144	144	144	144
	Mean cost (€)	603.96	88.97	175.19	868.12
	Total cost (€)	86,969.80	12,812.30	25,226.92	125,009.02
Total	N. patients	5,167	5,167	5,167	5,167
	Mean cost (€)	76.68	48.57	842.80	968.04
	Total cost (€)	396,181.86	250,943.31	4,354,750.42	5,001,875.59

ficacy of the treatment. Given the strength of the relationship between adherence to treatment and risk of refracture or death, and also in view of the high number of refractures and deaths that were not avoided, this is a worrying phenomenon.

The poor exposure and adherence to treatment was an unsatisfactory result in economic terms, too. Indeed, the mean cost increases observed in the patients who, according to indication, received drug treatment (+ € 256) or underwent a diagnostic test (+ € 40) were well offset by the sizeable reduction in refracture-related hospitalisation costs (- € 703). These results, which were replicated in patients treated with bisphosphonates and also found to be related to the different levels of adherence to treatment, appear particularly important given that this assessment was restricted to the first year following hip fracture – the pharmacological prevention already proved effective in this short period of time –, and also given that the prevention was not only *cost effective* but also *cost saving*, since the average total cost sustained for the treatment-adherent patient was lower than that sustained for the patient with unsatisfactory adherence.

The main limitation of this study was the absence, in the *administrative databases,* of certain patient data, such as race, socioeconomic status, anthropometric parameters and, above all, the results of the bone density and other tests necessary for disease staging and calculating patient risk. As a result, it was not possible to achieve complete control of confounding factors or, as a result, to exclude the effect of these parameters on event risk and on the healthcare costs of the different categories of exposure and adherence to treatment.

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