Reumatismo, 2012; 64 (1): 18-26

Adherence to therapeutic and diagnostic recommendations in patients with femur fracture and at risk of re-fracture or death: results of an analysis of administrative databases

L. Degli Esposti[1], L. Sinigaglia[2], M. Rossini[3], S. Adami[3], C. Cagnoni[4], C. Magliaro[5], C. Veronesi[1], S. Buda[1], S. Minisola[6]

[1]CliCon S.r.l. Health, Economics & Outcomes Research, Ravenna, Italy;
[2]Unità Operativa Complessa Reumatologia DH, Dipartimento di Reumatologia, Istituto Ortopedico Gaetano Pini, Milano, Italy;
[3]U.O. Reumatologia, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy;
[4]U.O. Medicina e Primo Soccorso di Bobbio, Piacenza, Italy;
[5]Servizio Controllo di Gestione ASL Caserta, Caserta, Italy;
[6]Medicina Interna, Università di Roma "Sapienza", Roma, Italy

SUMMARY

The aim of the present study was to evaluate the application into clinical practice of therapeutic and diagnostic recommendations for the prevention of bone re-fracture in postmenopausal women after an hospitalization for hip fracture in clinical practice and to assess the relationship between the application of diagnostic recommendations and re-fracture or death risk. A retrospective cohort analysis was conducted. All female patients, at least 65 years old, and with an hospitalization with main or secondary diagnosis of hip fracture during the period 1 January 2006 - 31 December 2008, were included. Besides demographic characteristics and comorbidities, drug treatment prescriptions related to bone fracture or supplementation with calcium or vitamin D and prescriptions of recommended laboratory and instrumental diagnostic tests (e.g. spine radiography), were analysed. A total of 5,636 patients were included in the study. The prescription of a drug treatment aimed to reduce the risk of re-fracture was found in 16.3% of patients, among them 76.3% (699 patients) used bisphosphonates only, 17.1% (157 patients) strontium ranelate only and 4.9% (45 patients) used more than one treatment during the observation period. Among the patients who did not receive drug treatment, 17.5% made use of only supplemental calcium and vitamin D. The remaining part of patients (69.1%) received no treatment. The prescription of at least one laboratory test of first and second level was performed, respectively, on 53.7% and 43.1% of included patients, whereas the prescription of at least one instrumental test of first and second level was performed, respectively, on 5.9% and 0.8%. Although it is established that the prescription of the recommended tests and appropriate drug treatment are significantly associated with reduced risk of re-fracture and death, today the application of these recommendations is reduced.

Key words: *Treatment adherence, pharmacoutilization, hip fracture, osteoporosis, refracture, death.*

Reumatismo, 2012; 64 (1): 18-26

INTRODUCTION

Osteoporosis is defined as a skeletal disorder characterized by an impairment of the mechanical resistance of the bone, causing an increased risk of fracture. This resistance is mainly a combination of bone density and quality (1). Therefore, a reduction in bone mass and microarchitecture results in fragile bones which fracture after light, that is low energy trauma. Fragile bone fractures are considered one of the major causes of morbidity and death worldwide (2), besides making a significant contribution to health care costs (3). In Italy, each year over 80,000 fractures of the proximal end of the femur are registered as being due to osteoporosis, with a net prevalence (72%) in women (3).

A number of guidelines describe different combinations of therapeutic and diagnos-

Corresponding author:
Dr. Luca Degli Esposti
CliCon S.r.l.
Via Salara, 36
48100 Ravenna, Italy
E-mail: luca.degliesposti@clicon.it

tic procedures to improve the prognosis of patients with femur fracture, and to reduce the risk of re-fracture and death (4, 5). These recommendations include the identification of subjects at high risk of re-fracture (e.g. patients with previous femur fracture), diagnostic, laboratory and instrumental tests, non-pharmacological measures of prevention and cure (e.g. calcium and vitamin D levels), indications for pharmacological treatment. In particular, these recommendations underline the importance of the diagnosis of osteoporosis by X-ray densitometry and analyze the contribution of multiple risk factors to the reduction of bone mass. Differential diagnosis of osteoporosis is extremely important, particularly in diseases with mechanisms which to a greater or lesser degree can increase the risk of fracture.

It is important that the patient undergoes a clinical examination and a series of simple 1st level biochemical tests to exclude secondary osteoporosis. These should include calcemia, creatinine phosphate, calciuria, serum protein fractionation, and ESR. According to guidelines, densitometry screening is recommended for all women after the age of 65 years. In spite of these therapeutic and diagnostic guidelines, very little scientific evidence has been transferred into clinical practice, and this has important clinical (6-16) and economic (17-22) implications.

The aim of this study was to measure the degree of transfer into clinical practice of these therapeutic and diagnostic recommendations for the prevention of bone re-fracture in post-menopausal women with femur fracture. The study also aims to evaluate the level of association between these recommendations (from now on referred to, in general, as *adherence to recommendations*) and the risk of re-fracture or death.

MATERIALS AND METHODS

Data sources

Data of study subjects were extracted from the databases of five local health authorities (LHA) in five regions of Italy: Lombardy, Emilia-Romagna, Tuscany, Campania and Calabria, with a total of two and a half million patients registered. In order to trace the assistance given, the local health authorities have various information flow systems for their local pharmaceutical services (LPS), direct pharmaceutical distribution (DPD), specialist visits (SV), hospital discharge records (HDR) and deaths. These systems allowed patients receiving these services to be traced.

Using appropriate data linkage procedures, it is possible to create a population databank containing individual, analytical and chronological profiles of all patients registered with the LHA. These databanks are known as administrative databanks and their role in the analysis of pharmacological utilization has been confirmed in numerous previous studies (23-25). In compliance with the laws on privacy, the patient's identity code was encrypted and those responsible for data management were not provided with any information which could lead to direct or indirect identification of the patient involved. The local ethics committees of all LHA participants were informed of the study according to the legal requirements concerning observational analysis.

Patients

This was a retrospective cohort analytical study involving all females aged 65 years or over with a hospitalization event with primary or secondary diagnosis of femur fracture (code ICD9: 820, 821) in the period from 1 January 2006 to 31 December 2008.

The date of hospital discharge was taken as the date of study enrollment. Patients admitted with a diagnosis of primary or secondary bone tumor, bone metastasis or pathological fracture were excluded from the study[1] (codes ICD9: 170, 198.5, 733.1).

[1]A pathological fracture is a case in which a skeletal segment which is already the site of either a previous pathological process or a pathological process in course has been subjected to light trauma, such as fractures at the site of tumors, osteomyelitis, etc.

Drug treatments

Study patients were classified as exposed or not exposed to drug treatment for bone fracture on the basis of the presence or absence of at least one prescription of bisphosphonates (codes ATC: M05BA e M05BB), strontium ranelate (code ATC: M05BX03), parathyroid hormones and analogs (code ATC: H05AA), calcitonin based drugs (code ATC: H05BA), raloxifene (code ATC: G03XC01), in the 12 months after discharge from hospital (observation period).

Calcium treatment (code ATC: A12AA), vitamin D (code ATC: A11CC), calcium and vitamin D in preconstituted solutions (code ATC: A12AX) was not classified as specific for femur fracture but was analyzed separately. Adherence to treatment was calculated in patients treated with bisphosphonates and strontium ranelate using the therapeutic indication in the accompanying drug leaflet.

The number of days covered by each prescription was calculated and added to the other prescriptions.

The total number of days covered was calculated in relation to the number of days in the observation period (365) and multiplied by 100.

The patients were classified into various levels of adherence to the therapeutic recommendations: *low adherence* if less than 40% days were covered; *intermediate* if between 41 and 80% days were covered; *high* if treatment cover was over 80%. Because of the low numbers, adherence to treatment was not calculated in patients exposed to other drug treatments (parathyroid hormones and analogs, calcitonin based drugs, raloxifene).

For those patients who died or were transferred to another LHA during the observation period, analysis of the drug treatment was carried out until the date of death or transfer.

Diagnostic tests

Study patients were classified as exposed or not exposed to diagnostic tests related to the bone fracture on the basis of the presence or absence of at least one prescription in the 12 months following the date of discharge from hospital (observation period). Diagnostic tests were classified into: *1st level laboratory tests* - ERA [code: 90.82.5], CBC [code: 90.62.2], fractionated serum proteins [code: 90.38.4], calcemia [code: 90.11.4], phosphoremia [code: 90.24.5], total alkaline phosphatase [code: 90.23.5], creatininemia [code: 90.16.3]); *2nd level laboratory tests* - ionized calcium [code: 90.11.6], TSH [code: 90.42.1], PTH [code: 90.35.5], 25OH-VitD [code: 90.44.6], cortisol [code: 90.15.3], immunofixation [code: 90.69.2], anti-gliadin, anti-endomysium, anti-tranglutaminase antibodies [codes: 90.48.06, 90.49.5, 90.49.7, 90.52.2, 90.53.6], transaminase [code: 90.09.2, 90.04.5], urinary electrophoresis proteins [code: 90.39.1], neoformation turnover [code: 90.24.1, 90.35.4, 90.37.7], resorption turnover [code: 90.16.7, 90.28.2, 90.36.6]); *1st level instrumental tests* - back X-ray [code: 87.23], umbocacral X-ray [code: 87.24], spine X-ray [code: 87.29], densitometry [code: 88.99.2, 88.99.3, 88.99.5]); *2nd level instrumental tests* - spine MRI [code: 88.93, 88.93.1], Spine CT scan [code: 88.38.1, 88.38.2]).

Statistical analysis

Data are expressed as mean ± standard deviation (SD) for continuous variables and as percentage for categorical variables. Pearson's X^2 test and one-way ANOVA were used to evaluate the differences in patients' characteristics according to exposure and adherence to treatment.

A Cox's regression model with estimated Hazard Ratio (HR) for adherence to the therapeutic and diagnostic recommendations was used to calculate the risk of death from any cause and risk of hospital admission, fatal and non-fatal, with primary or secondary diagnosis to fracture as follows: spine fracture [code ICD9: 805, 806], rib fracture [code ICD9: 807.0, 807.1], pelvis fracture [code ICD9: 808], humerus fracture [code ICD9: 812.0, 812.1, 812.2, 812.3, 812.4, 812.5], radio and ulnar fracture [code ICD9: 813.4, 813.5], femur fracture [code ICD9: 820],

tibia and fibula fracture [code ICD9: 823], ankle fracture [code ICD9: 824]).
Other covariates included in the model were: patient age, treatment with thiazide diuretics with associated formulations, with antiinflammatories, with gastroprotectors, with oral antidiabetics or statins, with previous osteoporosis treatment, femur fracture, cardiovascular problems, neoplasms, the presence of calcium or vitamin D supplements, presence of 1st level diagnostic tests, 2nd level diagnostic tests, 1st level instrumental tests, 2nd level instrumental tests, presence of specific drug treatment.
In order to exclude data resulting from the same fracture, patients with re-fracture of the femur within 45 days of discharge after the initial hospitilization event were excluded from the regression model.
$P<0.05$ was considered statistically significant. All analyses were carried out with SPSS software for Windows (SPSS Inc., Chicago, Illinois, USA), version 18.0.

RESULTS

A total of 5,686 patients were selected for the study. Of these, 50 patients (0.8% of selected patients) were excluded because they had been admitted with a diagnosis of bone tumor, bone metastasis or pathological fracture. Average age of the remaining 5,636 patients was 82.7±7.3 years (range 65-103 years).

Drug treatment

Exposure to drug treatment for the fracture (previous to and/or subsequent to the fracture) was reported in 16.3% of patients. Of these, 28.9% also presented treatment previous to the femur fracture (Table I). Just 4.6% of patients received only calcium or vitamin D supplements. Figure 1 shows the prevalence of the use of different drug treatments and calcium or vitamin D supplements in the period previous or subsequent to the femur fracture. Among patients exposed to drug treatment for bone fracture, 62.0% also received calcium or vitamin D supplements. Among those who, on the contrary, were not exposed to specific drug treatment, 17.5% received only calcium or vitamin D supplements (Table II).

Table I - Essential drug treatment before and after femur fracture.

	N.	%
No treatment	4,533	80.4
Only pre-fracture	187	3.3
Only post-fracture	651	11.6
Both pre- and post-fracture	265	4.7
Total	5,636	100

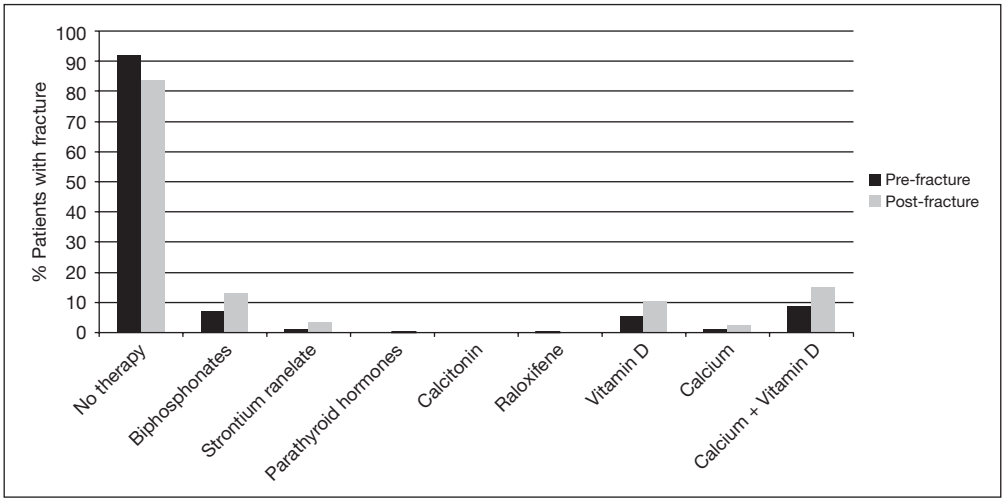

Figure 1 - Use of essential drug treatment and calcium or vitamin D supplements before and after femur fracture.

During the observation period, 699 patients (76.3% of patients exposed to specific drug treatment) used only bisphosphonates, 157 pazienti (17.1%) used only strontium ranelate, and 45 patients (4.9%) used more than one treatment (Table III). Of these last patients, 38 patients used bisphosphonates and and strontium ranelate. In this study, given the reduced number of patients with more than one treatment, the question as to whether this concerned treatment associated with others or substituting others was not explored (Table III).

In patients exposed to treatment with bisphosphonates in monotherapy, 41.3, 36.5 and 22.2% had *low*, *intermediate* and *high adherence* to treatment, respectively. In patients exposed to strontium ranelate in monotherapy, 55.4, 31.8% and 12.8% had low, intermediate and high adherence to treatment, respectively (Table IV).

Diagnostic tests

At least one 1st level laboratory test was prescribed in 53.7% of patients, at least one 1st level instrumental test in 43.1%,and at least one 2nd level instrumental test in 0.8% (Table V). Table V shows the number of patients who were prescribed at least one diagnostic test in the period previous and/or subsequent to

Table II - Essential drug treatment as monotherapy or associated with calcium or vitamin D supplements after femur fracture.

	Frequency	%
No osteoporosis medication	**4,720**	**83.7**
Neither osteoporosis medication nor calcium/vitamin D	3,895	82.5
Only calcium/vitamin D supplements	825	17.5
Osteoporosis medication	**916**	**16.3**
Only osteoporosis medication	348	38.0
Osteoporosis medication + calcium/vitamin D supplements	568	62.0
Total	**5,636**	**100.00**

Table III - Essential drug treatment in the observation period after femur fracture.

Treatment during observation period	N.	%
Bisphosphonates	699	76.3
Parathyroid hormone	13	1.4
Calcitonin based products	1	0.1
Raloxifene	1	0.1
Strontium ranelate	157	17.1
Multiple drug treatment (in association or as substitute)	**45**	**4.9**
Bisphosphonates – Parathyroid hormone	4	8.9
Bisphosphonates – Raloxifene	2	4.4
Bisphosphonates – Strontium ranelate	38	84.4
Parathyroid hormones – Strontium ranelate	1	2.2
Total	**916**	**100**

Table IV - Adherence to treatment in patients with femur fracture treated with bisphosphonates or strontium ranelate.

	Level of adherence						Total	
	<=40%		40-80%		>80%			
Biphosphonates (n %)	289	41.3	255	36.5	155	22.2	699*	100
Strontium ranelate (n %)	87	55.4	50	31.8	20	12.8	157*	100

*Patients in monotherapy.

Table V - Prescription of 1st and 2nd level laboratory tests and 1st and 2nd level instrumental tests before and after femur fracture (at 3 and 12 months post-fracture).

	1 year pre-fracture		3 months post-fracture		1 year post-fracture	
1st level laboratory tests[1] (n %)	**2,612**	**46.3**	**1,515**	**26.9**	**3,025**	**53.7**
2nd level laboratory tests[2] (n %)	**2,278**	**40.4**	**859**	**15.2**	**2,427**	**43.1**
1st level diagnostic tests[3] (n %)	**423**	**7.5**	**74**	**1.3**	**330**	**5.9**
Densitometry (n %)	77	1.4	15	0.3	105	1.9
Back X-ray (n %)	170	3.0	27	0.5	108	1.9
Lumbosacral X-ray (n %)	324	5.7	54	1.0	220	3.9
Spine X-ray (n %)	9	0.2	0	0.0	2	0.0
2nd level diagnostic tests[4] (n %)	**79**	**1.4**	**4**	**0.1**	**44**	**0.8**

[1]1st level laboratory tests; ESR, CBC, fractionated protiens, calcemia, phosphorus, total alkaline phosphatase, creatininemia. [2]2nd level laboratory tests: ionized calcium, TSH, PTH, 25OH-VitD, cortisol, immunofixation, anti-gliadin antibodies/anti-endomysium / anti-tranglutaminase, transaminase, urinary protein electrophoresis, neoformation turnover, resorption turnover. [3]1st level laboratory tests: spine X-ray, back X-ray, lumbosacral X-ray, densitometry. 42nd level laboratory tests: spine MRI, spine CT scan.

the femur fracture (in the three months before and in the 12 months subsequent to the fracture event).

Survival analysis

Multivariate survival analysis with reference to the year after the enrollment admission showed that a new admission for bone fracture was requested for 368 patients (femur, pelvis, ribs, ankle, tibia/fibula, humerus, spinal column, colonna vertebrale, radio/ulnar) and that there had been 1,083 deaths, with 92.1% and 80.5% of survival, respectively. Univariate survival anaylsis showed that the risk of re-fracture was significantly lower in patients exposed to drug treatment for osteoporosis (-53.3% [-67.3%; -33.2%] with respect to patients not exposed to treatment (P<0.001).

The multivariate model showed, among other factors, that the risk of re-fracture was significantly lower in patients treated with calcium or vitamin D supplements (-31.8% [-50.2%; -6.6%] with respect to patients who did not receive supplements (P<0.05), patients who received prescription of 1st level laboratory tests (-63.7% [-76.0%; -45.2%] with respect to those without prescription of diagnostic tests (P<0.001), in patients who received prescription of 1st level instrumental diagnostic tests (-72.1% [-89.7%; -24.8%] with respect to patients without prescription of diagnostic tests (P<0.05) and in patients with prescription of 2nd level laboratory tests (-37.3% [-60.5%; -0.5%] with respect to patients without prescription of diagnostic tests (P<0.05) (Table VI).

From a univariate survival model, the risk of death was significantly lower in patients with specific pharmacological treatment (-81.7% [-86.8%; -74.4%] with respect to the patients without treatment (P<0.001).

An analysis of the multivariate model, among other factors, shows that the risk of death is significantly lower in patients who received calcium or vitamin D supplements (-39.3% [-51.0%; -24.9%] with respect to patients who did not receive supplements (P<0.001), in patients who were prescribed 1st level instrumental diagnostic tests (-54.1% [-73.6%; -20.3%] with respect to patients who were not prescribed diagnostic tests (P<0.01), in patients who were prescribed 2nd level laboratory tests (-25.0% [-40.1%; -6.1%] with respect to patients who were not prescribed diagnostic tests (P<0.05), and in patients receiving specific drug treatment (-62.3% [-73.4%; -46.6%] with respect to patients not receiving treatment (P<0.001) (Table VII).

DISCUSSION

Results confirm that there is little transfer of diagnostic and therapeutic recommendations into clinical practice for the prevention of bone re-fracture in post-

menopausal patients with femur fracture. With respect to most studies in this field, (13-15) the present analysis examined adherence to diagnostic recommendations and showed that far fewer 1st and 2nd level laboratory and instrumental tests were prescribed than are suggested in available guidelines (4, 5). In particular, prescription of laboratory tests was low (53.7% and 43.1% of patients were prescribed, respectively, 1st and 2nd level tests) and very low for instrumental tests such as X-rays and densitometry (5.9% and 0.8% patients were prescribed, respectively, 1st and 2nd level tests).

In addition, there was no increase in the number of patients who were prescribed a diagnostic test in the period after the fracture with respect to the period before the fracture (from 46.3 to 53.7% for 1st

Table VI - Predictors of risk of bone re-fracture in patients with femur fracture.

	HR	IC 95,0% per HR		P
		Lower	Higher	
Patient age	0.989*	0.975	1.002	N.S.
Treatment with thiazide diuretics in preconstituted association** (presence)	0.332	0.204	0.541	<0.001
Treatment with antiinflammatories** (presence	0.353	0.221	0.563	<0.001
Treatment with gastroprotectors** (presence)	0.378	0.282	0.506	<0.001
Treatment with oral antidiabetic** (presence)	0.416	0.221	0.783	< 0.01
Previous osteoporosis medication (presence)	2.308	1.629	3.270	<0.001
Previous admission for femur fracture (presence)	0.632	0.235	1.697	N.S.
Treatment with statins** (presence)	0.660	0.338	1.289	N.S.
Treatment with calium/vitamin D supplements (presence)	0.682	0.498	0.934	<0.05
1st level diagnostic tests (presence)	0.279	0.103	0.752	<0.05
1st level laboratory tests (presence)	0.363	0.240	0.548	<0.001
2nd level laboratory tests (presence)	0.627	0.395	0.995	<0.05
Osteoporosis medication (presence)	**0.705**	**0.471**	**=1.053**	**=0.088**

*HR relative to an annual age increase. **During the observation period. Presence of 2nd level diagnostic tests was inserted as covariate analysis but the low number of cases meant a convergence model could not be produced; this was, therefore, removed from the analysis.

Table VII - Predictors of risk of death of patients with femur fracture.

	HR	IC 95.0% per HR		P
		Lower	Higher	
Patient age	1.054*	1.045	1.063	<0.001
Treatment with thiazide diuretics in preconstituted association**	0.190	0.124	0.290	<0.001
Treatment with antiinflamatories**	0,444	0,335	0.589	<0.001
Treatment with gastroprotectors**	0.711	0.612	0.827	<0.001
Treatment with oral antidiabetics**	0.601	0.434	0.834	<0.01
Previous osteoporosis treatment	1.186	0.921	1.527	N.S.
Previous admission for femur fracture	0.375	0.178	0.791	=0.01
Treatment with statins**	0.259	0.138	0.484	<0.001
Previous admission for cardiovascular problems	1.807	1.552	2.104	<0.001
Admission for neoplasms	3.430	2.786	4.222	<0.001
Calcium/vitamin D supplements	0.607	0.490	0.751	<0.001
1st level diagnostic tests	0.459	0.264	0.797	<0.01
2nd level diagnostic tests	0.670	0.093	4.796	N.S.
1st level laboratory tests	0.863	0.701	1.062	N.S.
2nd level laboratory tests	0.750	0.599	0.939	<0.05
Osteoporosis treatment	**0.377**	**0.266**	**0.534**	**<0.001**

*HR related to annual age increase. **During the observation period.

level laboratory tests, from 40.4 to 43.1% for 2nd level laboratory tests, from 7.5 to 5.9% for 1st level instrumental tests, from 1.4 to 0.8% for 2nd level instrumental tests).

As far as exposure to drug treatment is concerned, a low percentage of patients with femur fracture were prescribed drugs for osteoporosis (16.3%), another low percentage of patients were only prescribed calcium and vitamin D supplements (14.6%), while 69.1% were not prescribed any type of treatment.

These results are in line with previous studies (13-16, 22) and are important, above all, in this study cohort of patients who, having had a previous fracture event, are already at a particularly high risk of new fragile fracture. Adherence to treatment is a further problem. In fact, of the patients exposed, only a quarter had adequate therapeutic cover.

The second important result from this study is the extent of the relationship between application of the therapeutic and diagnostic recommendations and the risk of re-fracture or death in post-menopausal patients with femur fracture.

In accordance with previous studies, (6-12) treatment for osteoporosis was protective and had an impact, above all, on total mortality (-62.3% of risk with respect to patients not undergoing treatment). Calcium and vitamin D supplements were also protective (-31.8 and -39.3% of risk, respectively, of re-fracture and death, with respect to patients not receiving supplements). Besides drug treatment, the present study analyzed the effect of prescription of the recommended diagnostic tests. The prescription of 1st level instrumental tests such as X-rays (back, lumbosacral, and spine) and densitometry is associated with a -72.1% reduction in re-fracture risk and a -54.1% reduction in death risk (respect to patients who were not prescribed these tests). It would be quite reasonable to attribute this to an increased awareness of the real condition of the patient and to the appropriate therapeutic strategies which were consequently adopted.

The main limitation of this study was that some clinical information concerning patients was not available in the administrative information flow systems which are currently used.

The most important information which was missing concerned the severity of osteoporosis.

Since in clinical practice the severity of osteoporosis is in itself a factor which increases the need for drug treatment and diagnostic tests, the socio-economic status, anthropometric parameters and, above all, the study of the relationship between adherence to therapeutic and diagnostic recommendations and the risk of re-fracture (in cases in which the severity of the osteoporosis was not recorded) could not explained why each individual parameter contributed to the risk of re-fracture or death. In particular, the lack of confirmation of a diagnosis of osteoporosis could have led to the inclusion of patients with traumatic and not osteoporotic fracture.

However, selection criteria in the study cohort meant only female patients aged over 65 years were included and this should have minimized such a risk. Selection criteria with particular reference to previous femur fracture, should also have limited any possible bias in the therapeutic indications, since these patients, precisely because of the fracture event, were in any case exposed to a continuative preventive treatment (*confounding by indication*).

REFERENCES

1. NIH Consensus Development Panel on Osteoporosis. 2001.
2. Johnell O. The socioeconomic burden of fractures: today and in the 21st century. Am J Med. 1997; 103: 20S-26S.
3. Piscitelli P, Brandi ML, Tarantino U, et al. Incidenza e costi delle fratture di femore in Italia: studio di estensione 2003-2005. Reumatismo. 2010; 62 (2): 113-8.
4. Tarantino U, Resmini G. La gestione delle fratture da fragilità ossea. Raccomandazioni per chirurghi ortopedici. Sprinter Italia. 2011.
5. Linee guida per la diagnosi, prevenzione e terapia dell'osteoporosi. SIOMMS. Reumatismo. 2009; 61 (4): 260-84.
6. Caro JJ, Ishak KJ, Huybrechts KF, et al. The impact of compliance with osteoporosis

therapy on fracture rates in actual practice. Osteoporos Int. 2004; 15: 1003-8.
7. Gallagher AM, Rietbrock S, Olson M, et al. Fracture outcomes related to persistence and compli- ance with oral bisphosphonates. J Bone Miner Res. 2008; 23: 1569-75.
8. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006; 38: 922-8.
9. Penning-van Beest FJA, Van den Boogaard CHA, Erkens JA, et al. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporosis Int. 2008; 19: 511-7.
10. Rossini M, Bianchi G, Di Munno O, et al. Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int. 2006; 17: 914-21.
11. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc. 2006; 81: 1013-22.
12. McClung MR. Bisphosphonates in osteoporosis: recent clinical experience. Expert Opin Pharmacother. 2000; 1: 225-38.
13. Van den Boogaard CHA, Breekveldt-Postma NS, Borggreve SE, et al. Persistent bisphosphonate use and the risk of osteoporotic fractures in clinical practice: a database analysis study. Curr Med Res Opin. 2006; 22: 1757-64.
14. Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. Curr Med Res Opin. 2005; 21: 1453-60.
15. Penning-van Beest FJA, Goettsch WG, Erkens JA, Herings RMC. Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. Clin Ther. 2006; 28: 236-42.
16. Carnevale V, Nieddu L, Romagnoli E, et al. Osteoporosis intervention in ambulatory patients with previous hip fracture: a multicentric, nationwide Italian survey. Osteoporosis Int. 2006; 17: 478-83.
17. Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007; 22 (3): 465-75.
18. Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. Nat Rev Rheumatol. 2010; 6 (2): 99-105.
19. Lippuner K, von Overbeck J, Perrelet R, et al. Incidence and direct medical costs of hospitalizations due to osteoporotic fractures in Switzerland. Osteoporos Int. 1997; 7: 414-25.
20. Lohnell O. The socioeconomic burden of fractures: today and in the 21st century. Am J Med. 1997; 103: 20S-25S.
21. Rossini M, Piscitelli P, Fitto F, et al. Incidenza e costi delle fratture di femore in Italia. Reumatismo. 2005; 57 (2): 97-102.
22. Tarantino U, Ortolani S, Degli Esposti L, et al. Analysis of the costs and consequences of adherence to therapy in hip fracture patients. Results of a longitudinal analysis of administrative databases. Clinical Cases in Mineral and Bone Metabolism. 2011; 8 (1): 61-6.
23. Motheral BR, Fairman KA. The use of claims databases for antihypertensive drugs and associated hospitalization. Clin Ther. 1997; 19 (2): 346-66.
24. Birnbaum HG, Cremieux PY, Greenberg PE, et al. Using health care expenditures for healthcare claims data for outcome research and pharmaco-economic analyses. Pharmacoeconomics. 1999; 16: 1-8.
25. Degli Esposti L, Valpiani G, Baio GL. Valutare l'efficacia degli interventi in sanità. Guida alla raccolta ed alla gestione dei dati clinici ed amministrativi. Il Pensiero Scientifico. Roma, 2002.