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The economic burden of severe osteoporotic fractures in the French healthcare database: the FRACTOS study

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Conflicts of interests

AC and LP are employees of UCB Pharma SA. GB and CC are employees of IQVIA, and FM was an employee of IQVIA at the time of the study, a contract research agency responsible for the operational management of the study, funded by UCB Pharma SA.

CR has received grants or honoraria from Alexion, Amgen, Regeneron and UCB. TT has received consultancy/speaker's fees from Amgen, Arrow, Biogen, Chugai, Expanscience, Grunenthal, Jansen, LCA, Lilly, MSD, Nordic, Novartis, Pfizer, Sanofi, Thuasne, Theramex, TEVA and UCB and financial support or fees for research activities from: Bone Therapeutics, Chugai, UCB; JP has received honoraria from Amgen, MSD, Eli Lilly, Novartis, Pfizer and UCB. FT is head of the Centre de Pharmacoépidémiologie (Cephepi) of the Assistance Publique – Hôpitaux de Paris and of the Clinical Research Unit of Pitié-Salpêtrière hospital, both these institutions have received unrestricted research funding and grants for the research projects handled and fees for consultant activities from a large number of pharmaceutical companies, that have contributed indiscriminately to the salaries of its employees. FT is not employed by these institutions and has not receive any personal remuneration from these companies.

Data availability

The study was performed in the SNDS database, which managed by the French national health insurance fund, the CNAMTS (*Caisse nationale de l'assurance maladie des travailleurs salariés*). Access to the database to institutions who meet the criteria for access to confidential data is permitted. Applications should be made to the National Health Data Institute (INDS; 19 rue Arthur Croquette, 94220 Charenton-le-Pont, Telephone: +33 1 45 18 43 90; Email: contact@indsante.fr; Website: <https://www.indsante.fr/fr>), which is responsible for access to all health data in France and is a one-stop-shop window for access to the SNDS database.

Abstract

Osteoporosis carries a high medical, economic and societal burden principally due to the risk of severe fractures. The objective of this cost-of-illness study was to describe health resource utilization and associated costs in all patients aged ≥ 50 years hospitalized for a severe osteoporotic fracture over a six-year period (2009-2014) in France. Data were extracted from the French national healthcare database (SNDS) on all healthcare resource utilization between the index date (date of hospitalization for first fracture during the enrolment period) and study end (31st December 2016), or until the patient died. Costing was restricted to direct costs and determined from the payer perspective. Variables related to costs were identified through multivariate logistic regression analysis. 356,895 patients were included (median follow-up: 39.1 months). In the year after the index fracture, 36,622 patients (10.5%) were rehospitalized for a fracture-related reason. Only 18,474 (5.3%) underwent bone densitometry and 58,220 (16.7%) received a specific treatment. The total annual *per capita* osteoporosis-related cost in the year following the index severe osteoporotic fracture was €18,040 (from €8,598 for multiple ribs to €21,085 for hip fracture) of which €17,905 was incurred by fracture-related costs. The cost incurred by management of osteoporosis was €135. Over Years 2-5, the mean annual *per capita* costs of fracture treatment (€806, mostly attributable to the treatment of refractures) continued to dominate those of osteoporosis management (€99). Total annual cost of care was €1,260 million (Year 2014). Variables associated with higher cost were older age, male gender, site of fracture, a history of prior osteoporotic fracture and the number of refracture events. The five-year cost of severe osteoporotic fractures to the French healthcare system is high and mostly attributable to the treatment of refractures. Improved fracture prevention measures in patients with osteoporosis is crucial to reduce the economic burden of the disease.

Keywords: Health Economics, Osteoporosis, General population studies, Therapeutics, Fracture prevention.

Introduction

Information on the current economic burden of severe osteoporotic fractures in France is limited. In a European-wide survey of the medical management, epidemiology and economic burden of osteoporosis conducted by the International Osteoporosis Foundation (IOF), it was estimated that around 380,000 new severe osteoporotic fractures occurred in France in 2010.⁽¹⁾ We have recently performed a study in the French national healthcare database (*Système National des Données de Santé: SNDS*) with the goal of identifying and characterizing all patients hospitalized in France for a severe osteoporotic fracture over a six-year period.⁽²⁾ In our study, the prevalence of severe osteoporotic fractures was higher than the IOF estimate, with around half a million individuals identified, corresponding to 83,000 new fractures a year and a crude annual incidence rate of ~3.6 cases /1,000 in the population ≥ 50 years of age.⁽²⁾

Currently, most of the available primary data on the cost of osteoporosis in France are restricted to hospitalization and rehabilitation costs for specific fracture types.⁽³⁻⁵⁾ An overview of the burden of fragility fractures in six European countries, including France, estimated the mean cost in the year following fracture to be €12,856 for hip fractures and €3,205 for vertebral fractures; with a direct cost of incident fracture in 2017 reported to be €3,748 million.⁽⁶⁾ These cost estimates are lower than those measured directly in the ICUROS study, a recent prospective microcosting study conducted in France,⁽⁷⁾ in which total direct and indirect costs over eighteen months (including initial fracture-related costs and follow-up costs) were €23,926 for hip fractures (€15,951 *per annum*) and €14,561 for vertebral fractures (€9,707 *per annum*). The inconsistency between the findings of these different studies emphasizes the need for a more comprehensive evaluation of the economic burden related to osteoporosis and -fracture management. Administrative health insurance databases are an important resource for conducting such outcomes research in general and cost-of-illness studies in particular.⁽⁸⁾ They allow real-world disease management to be described faithfully and, in countries with comprehensive national health insurance coverage, such as France, with exhaustive patient identification, thus minimizing the risk of selection bias or recall bias, and providing high statistical power for analysis. In this respect, our study in the SNDS provides an opportunity to collect exhaustive data on healthcare resource utilization and costs in a large sample of individuals hospitalized with severe osteoporotic fractures. The objective of this study was to describe health resource utilization and associated costs collected in the FRACTOS study in all patients aged ≥ 50 years hospitalized for a severe osteoporotic fracture over a six-year period (2009-2014) in France.

Methods

This cost of illness study uses data from the FRACTOS study, a retrospective cohort study performed within the SNDS database, the French national healthcare database.^(9,10) The SNDS database covers all reimbursed healthcare expenditure in both the public and private sectors for >99% of the French population. The scope of the study was patients with severe osteoporotic fractures defined as fractures of the hip, pelvis, proximal humerus, vertebrae or multiple ribs, and requiring hospitalisation. The rationale for the choice of these fracture sites is that they are associated with an elevated mortality risk.^(11,12) However, vertebral or rib fractures which did not require an overnight hospital stay were *de facto* excluded.

The study cohort was composed of all patients ≥ 50 years hospitalized for management of a severe osteoporotic fracture over a six-year period between 1st January 2009 and 31st December 2014. The design and methodology of the FRACTOS study have been described in detail previously⁽²⁾ and are summarized briefly below.

In the present analysis, we followed all patients from the date of the first hospitalization for a severe osteoporotic fracture during the inclusion period (the index date up to the study end on 31st December 2016), or until the patient died (a maximum period of eight years). For patients experiencing multiple fracture events, the first event documented was considered to be the index fracture, and subsequent events were considered refractures (recurrent fractures). All healthcare resource utilization over this post-index period was documented. The cost analysis was performed from the perspective of the payer and covered all healthcare resource expenditure reimbursed by the national health insurance. Accrued costs were evaluated at the horizons of one and five years.

Participants

All patients aged ≥ 50 years hospitalized for a severe osteoporotic fracture during the inclusion period were enrolled. Severe osteoporotic fractures were identified from the ICD-10 disease classification codes in the hospital discharge summaries. These codes are listed in Supplementary Table 1. Patients with fractures at multiple sites and those with osteoporosis with current pathological fracture (ICD-10 code M80) were excluded, since the cost could not be assigned unequivocally to a specific index fracture.

Patients with other medical conditions that could account for the fracture or its care were ineligible. These included Paget's disease, any cancer, infectious arthritis, planned surgical interventions (including elective orthopedic surgery or interventions involving care of a prosthesis), or identified traumatic injury. However, patients treated with glucocorticoids could be included. The corresponding ICD-10 codes are listed in Supplementary Table 1. In

addition, patients who changed their insurance regimen during the data collection period were excluded since exhaustive documentation of healthcare resource utilization throughout the period could not be guaranteed.

Data extraction

At the time of the index hospitalization, age, gender, health insurance status and municipality of residence were documented. During this post-index period, information was collected on all hospital and community healthcare resource utilization until the end of the follow-up period. This included data on inpatient or outpatient visits, rehabilitation care, home care, consultations with general practitioners (GPs) or community-based specialists such as rheumatologists, surgeon visits, paramedical care (for example, nurse visits, physiotherapy or occupational therapy), investigations (for example, X-rays, dual-energy X-ray absorptiometry (bone densitometry) or blood tests), medical devices, medications and reimbursed medical transplantation. It should be noted that, for consultations in hospitals, the specialty of the physician consulted is not identified in the SNDS. In addition, data on physiotherapy sessions were only available for the number of outpatient physiotherapy sessions in the community once the patient has been discharged from hospital. Refracture events at any site were documented throughout the post-index period.

The database was also searched backwards for three years prior to 2009 (pre-index period) to collect historical data on confounding pathologies that might also account for the fracture and to document any previous severe osteoporotic fractures that may have occurred prior to the enrollment period. Patients with confounding pathologies were excluded (see above), but not those with previous fractures. Any delivery of specific or non-specific osteoporosis treatments during the pre-index period was also documented.

Medications considered as specific anti-osteoporotic medications were those available at the time of the study, namely bisphosphonates (etidronate, alendronate, risedronate, ibandronate or zoledronic acid), raloxifene, teriparatide, denosumab, strontium ranelate and hormone replacement therapy (HRT). Strontium ranelate was not evaluated since it was no longer reimbursed (and thus no longer documented in the SNDS) in 2015 and withdrawn from the market two years later. Prescriptions for calcium or vitamin D, which are not considered to be specific anti-osteoporosis treatments, were also documented. A full list of healthcare resources documented is provided in Supplementary Table 2.

Derived variables

Osteoporotic treatment duration was determined as the time between the first documented delivery of medication and the end of the theoretical treatment period covered by the last

delivery (or until the end of the study or until the patient died) without treatment interruption. A treatment was considered to be interrupted if the interval between the theoretical end of a treatment and the next treatment dispensation was >90 days.

Healthcare resource utilization

Healthcare consumption was quantified by type of expense and by year of follow-up. Consumption was divided into three categories, namely consumption related to the fracture itself, consumption related to management of osteoporosis and unrelated consumption (including consumption related to comorbidities). Resources entering into the first two categories are listed in Table 1. All other items were considered unrelated healthcare consumption, and these data are not presented in the present report.

Costing

Costing was restricted to direct costs and was determined from the perspective of the payer (national health insurance). The proportion of cost reimbursed by national health insurance varies according to the type of expense. For example, medications delivered in the community are reimbursed at 15%, 30% or 65%, depending on the benefit that the medication provides, whereas imaging procedures are reimbursed at 70% to 100% and surgery at 100%. Certain patients are eligible for full reimbursement on the grounds of long-term illness or low income; these patients were identified and the full cost of their care was taken into account in the analysis.

Costs to the payer for medical procedures, consultations and medications were attributed from official French national tariffs for medical procedures, healthcare consultations and medication defined by the Economic Committee for Medicinal Products and are expressed in 2018 Euros, adjusted on the basis of the consumer price index. Costs of hospitalization by type of hospital stay for public hospitals and private clinics were determined based on hospital expenditure reimbursed to the hospital. Each hospital stay was identified by a diagnosis-related group based on the reason for hospitalization described in the hospital discharge summary. Each diagnosis-related group is attributed a specific fixed tariff covering all estimated costs of hospitalization, including medical procedures, drugs and medical devices delivered in hospital during hospital stay. Each discharge summary also provides a severity qualifier (ranging from 1 to 4) for the stay, which is taken into account in the cost tariffication of the stay. Some expensive drugs and innovative medical technologies (for example, immunotherapies and cancer targeted therapies) specified on a nominative list are costed and reimbursed apart, and these costs were also integrated. Annual *per capita* costs were determined by type of expenditure and overall. Specific costs of healthcare consumption

related to the fracture itself and of consumption related to management of osteoporosis (as defined in Supplementary Table 3) were determined.

Statistical analysis

Data on healthcare resource utilization were analyzed for the follow-up population, consisting of all members of the analysis population with at least one day of follow-up after the index hospitalization. Two time horizons were considered, namely the year following the index hospitalization and the five years following the index hospitalization. For the latter, only those patients for whom five full years of follow-up were available were considered.

Healthcare consumption is presented as the number (and percentage) of patients using the resource at least once. For each individual patient, all costs engendered were consolidated by type of expenditure. These individual patient costs were aggregated across the cohort to generate a *per capita* cost for each type of expenditure. All costs are presented as mean with standard deviation (SD) (and, where appropriate, median with interquartile range [IQR]) *per capita* costs. Persistence with treatments taken after the fracture was evaluated from the time the treatment was started using Kaplan-Meier survival analysis.

A generalized linear model with an identity link function and a gamma distribution was performed to identify variables potentially associated with total cost over five years as a continuous variable. This analysis was performed on the patient population for whom five complete years of data were available. Independent categorical variables tested in the model were age (by class), gender, site of the index fracture, number of refractures (0, 1 or >1) and fracture history prior to the index fracture. Associations with cost were presented as risk ratios (RR) with their Wald 95% confidence intervals (95%CI). All analyses were performed using SAS[®] software Version 16.2 (SAS Institute, Cary, USA).

Ethics

The study was conducted in accordance with relevant international and French regulatory requirements. Use of the SNDS database for this type of study is regulated by the National Health Data Agency (*Institut National des Données de Santé*). The FRACTOS study was authorized by the CEREEES (the French expert ethical committee for health technology studies and evaluations) in February 2018 and by the French national data protection agency (Commission Nationale de l'Informatique et des Libertés) in March 2018.

Results

Study population

Overall, 560,499 patients with at least one hospitalization for severe osteoporotic fracture were identified in the SNDS database (General Regimen) from 2009 to 2014 of whom, 356,895 (63.7%) fulfilled the eligibility criteria. The principal reasons for exclusion were the presence of a confounding pathology or being aged under fifty years (Figure 1). Notably, 93,259 patients were ineligible as they had a documented diagnostic code for a malignant neoplasm before or after the index date from 2006 to 2016 inclusive. Data on healthcare consumption was available for 347,784 patients (97.4%) during the first year of follow-up and for 136,929 (38.4%) during five years of follow-up (Figure 1). The median duration of follow-up was 39.1 months (IQR: 21.8-60.5). The number of patients retained in the study, deceased or refractured by year of follow-up is presented in Supplementary Table 4.

The characteristics of the analysis population have been described previously⁽²⁾ and are provided for information in Supplementary Table 5. Index hospitalizations were mostly related to hip fractures, which accounted for 60% of all index hospitalizations. Four percent of patients had been previously hospitalized for a fracture in the three years preceding the index hospitalization, and 17.0% had been prescribed a specific osteoporosis treatment at least once before the index fracture. The mean age \pm SD of the analysis population was 78.8 ± 12.0 years, being around a decade older in patients with hip or pelvis fractures. Three-quarters of the patients were women (74.5%), except for multiple rib fractures, which most frequently occurred in men.

Healthcare resource utilization

In the year following the index fracture, all patients had been hospitalized for a severe osteoporotic fracture at least once (by definition) and 36,222 (10.5%) had been rehospitalized during the same year (Table 1). Rehospitalizations were motivated either by a new fracture, irrespective of site or severity, which occurred in 19,856 (5.6%) of these patients (Supplementary Table 4) or by post-surgical management of the original fracture.

Following a fracture-related hospitalization (index fracture or refracture), 46.4% of patients (N = 161,320) were discharged to a rehabilitation unit within the year following the index fracture. This was most frequently the case for patients with hip (55.9% of patients) or pelvis fractures (53.6%) compared to patients with vertebral (21.3%) or multiple rib fractures (12.4%) (Table 1). A similar overall proportion of patients (48.4%) participated in physiotherapy sessions within three months of their hospitalization. This proportion varied considerably between fracture sites, being lowest for multiple rib fractures (19.4%) and

highest for proximal humerus fractures (70.6%) (Table 1). The mean annual number of physiotherapy sessions also varied according to the fracture site, from 2.5 ± 6.7 for multiple rib fractures to 13.9 ± 13.5 for proximal humerus fractures (Table 1).

In subsequent years, the proportion of patients undergoing a fracture-related hospitalization decreased to a plateau of around 4% per year for the remainder of the follow-up period (Figure 2).

Regarding specific osteoporosis management during the first twelve months of follow-up period, 7.6% of patients consulted a community-based rheumatologist, this proportion ranged from 6.0% for patients with a hip fracture to 13.8% for those with vertebral fractures (Table 1). Overall, 18,474 patients (5.3%) underwent bone densitometry during this period. This rate was similar between fracture types, with the exception of patients with vertebral fractures, of whom 12.9% underwent bone densitometry (Table 1). In the following years, the proportion of patients undergoing densitometry decreased to 1.9% from Year 3 onwards (Figure 2).

Visits to GPs at which a prescription was made for a specific osteoporosis treatment or calcium or vitamin D supplementation were identified. These consultations were made by 138,566 patients (39.8%) of in the year following the index hospitalization (Table 1). During this period, 58,220 patients (16.7%) received a specific osteoporosis treatment delivered from a community pharmacist, most frequently patients with vertebral fractures (25.8%). Of these treated patients, 21,228 (36.5%) had never been delivered a specific osteoporosis treatment during the pre-index period and were thus considered treatment-naïve. The specific treatments delivered to these treatment-naïve patients were most frequently bisphosphonates (in 83.0% of patients initiating a specific treatment; Supplementary Table 6), principally alendronate (N = 11,697; 36.2% of newly-treated patients). In addition, 4,707 patients received strontium ranelate (14.6%) and 3,709 received HRT (11.5%). The other specific treatments were each used by less than 1,000 patients (6%). In contrast, calcium or vitamin D supplementation (or both) was prescribed to 86.4% of these newly-treated patients (N = 74,858).

For treatment-naïve patients delivered a specific osteoporosis treatment following the index hospitalization, the median treatment persistence with the first-line treatment was 13 weeks after the first delivery. A Kaplan-Meier persistence curve is presented in Figure 3. The proportion of patients continuously under treatment was 49.0% [95% CI: 48.6% – 49.3%] at Year 1, 31.7% [31.3% – 32.0%] at Year 2 and 12.9% [12.6% – 13.2%] at Year 5.

Cost

During the year following the index hospitalization for a severe osteoporotic fracture, the total annual *per capita* osteoporosis-related cost to public health insurance of these patients was

€18,040, of which the majority (€17,905) was incurred by treatment of the fracture (ranging from €8,474 for multiple rib fractures to €20,964 for hip fractures) (Table 2). Most of this expenditure corresponded to the cost of hospitalization (Table 3). In comparison, the costs incurred by management of osteoporosis were much lower, ranging from €122 for hip fractures to €213 for vertebral fractures. The principal contributors to these management costs were GP consultations for prescription of osteoporosis medication (37.0% of management costs), medication (28.9%) and blood tests (25.2%) (Table 3). This mean *per capita* cost of management of osteoporosis was relatively similar across fracture types, with the exception of vertebral fractures, which incurred higher management costs, principally attributable to a higher expenditure on osteoporosis medication. Patients with vertebral fractures also incurred higher costs (around two-fold higher than for hip fracture) for bone densitometry and for community-based rheumatologist visits (data not shown), although these cost items contribute only marginally to the total cost. *Per capita* costs of management of osteoporosis were lower in men than in women (€106 vs €146), the difference being accounted for principally by lower spending on medication (Table 3). In contrast, hospitalization costs were higher for men than for women (Table 3).

Over the following years, the costs of both fracture treatment and osteoporosis management decreased (Figure 4). The mean annual *per capita* cost of fracture treatment in subsequent years of follow-up was €806 and these costs were incurred principally as a result of a small number of refracture events and of hospital readmissions for care or complications of the original fracture treatment. Although the absolute costs incurred by management of osteoporosis decreased progressively in the years following the index hospitalization (from a mean *per capita* cost of €135 in Year 1 to €99 in Year 5), the cost structure remained essentially the same over time.

By multiplying the mean *per capita* cost by the total number of patients with severe osteoporotic fractures, the total cost to national health insurance of osteoporosis-related healthcare management can be estimated at €1,260 million for the year 2014. This included €1,230 million for fracture-related costs and €29 million for the costs of osteoporosis management.

Variables associated with cost

In the multivariate analysis, all variables evaluated were significantly associated with the mean total five-year cost of severe osteoporotic fractures. Variables associated with higher cost were older age, male gender, site of fracture (highest cost for hip fractures, lowest cost for multiple rib fractures), and a history of osteoporotic fracture (Figure 5).

Discussion

This study provides an estimate of the total direct medical costs associated with severe osteoporotic fractures in France. With an annual *per capita* cost of fracture and osteoporosis management of €18,040 in the year following the fracture and, on average, over 75,000 severe osteoporotic fractures requiring hospitalization occurring annually,⁽²⁾ the total direct annual medical cost of these fractures to the French public health system was estimated to have been around €1.26 billion in 2014. This is higher than the reported direct medical cost of management of acute coronary artery disease in France (€770 million in 2013), comparable to those of management of chronic heart failure (€1.2 billion in 2013) and somewhat lower than those of acute stroke (€3.5 billion in 2013).⁽¹³⁾

The cost findings can also be compared with a previous study of the cost of osteoporosis in the French National Hospital Database (PMSI) in 2008, which included women aged ≥ 50 years, principally with hip fracture.⁽⁴⁾ This earlier study reported a lower overall cost for hospitalization (€415 million) and for follow-up and rehabilitation stays (€331 million). In addition, mean annual *per capita* costs of hospitalization were lower (€6,127) than in FRACTOS although rehabilitation costs were higher (€10,546).⁽⁴⁾ This difference can be explained, at least in part, by the inclusion of patients with osteoporosis but without fracture, in the study of Maravic et al.⁽⁴⁾ In 2001, median in-patient *per capita* costs for hip fracture in €8,727 and an overall cost to the health system for all severe osteoporotic fractures of €715 – €763 million,⁽⁵⁾ around half the cost reported in the present study.

Our data are more consistent with recently published data from the ICUROS study, which reported total costs over 18 months following index fracture of €23,926 for hip fracture and €14,561 for vertebral fracture.⁽¹⁴⁾ The FRACTOS AND ICUROS studies were performed contemporaneously but used two quite different approaches. ICUROS was a micro-costing study in which costs are documented prospectively over 18 months in a relatively small number of patients with fragility fractures (N = 431) recruited from six specialist osteoporosis departments in university hospitals. Our FRACTOS study, was a retrospective study evaluating, in principle, all patients hospitalized for an osteoporotic fracture in France (N = 356,895) over a follow-up period of 2 to 8 years. Due to the way the data was collected, ICUROS should capture osteoporosis-related costs more accurately, but the representativeness of the findings for all patients with osteoporotic fractures in France may be questionable as the study was performed only in six tertiary centers. In contrast, the FRACTOS study documents in principle all patients with severe osteoporotic fractures in France and thus should capture all reimbursed osteoporosis care. On the other hand, as we do not have access to the medical records in FRACTOS, we had to make assumptions about which costs were attributable to osteoporosis (for example, we assumed that all visits to

rheumatologists were related to osteoporosis). The two approaches are thus complementary, and the fact that they provide consistent findings provides strong evidence that the real cost burden of osteoporosis and related-fractures in France is much higher than described in previous estimates,^(1,6) which, in the absence of recent reliable data, were based on extrapolations from fragmented data from different sources.

Within the year following the index hospitalization, the fracture-related costs dominated expenditure on osteoporosis, accounting for >95% of costs. Compared to the cost of acute fracture care, the *per capita* cost of osteoporosis management was much lower (€122 to €213 in the year following the fracture, depending on the fracture site). The cost of osteoporosis management is intrinsically lower than that of fracture management, as care can be provided in the community without the need for hospitalization. However, the low level of expenditure is also explained by the low number of patients who are being managed for their osteoporosis *per se*. For example, in the year following hospitalization for a severe osteoporotic fracture, only 8% of patients consulted a community rheumatologist, 5% underwent bone densitometry and 17% received a specific osteoporosis treatment. Although 40% consulted a GP in relation to their osteoporosis (as identified through prescription and delivery of a specific or non-specific osteoporosis treatment), in most cases this only resulted in a prescription for calcium or vitamin D supplementation. These findings indicate that the quality of osteoporosis management after a fracture in terms of assessment and treatment of osteoporosis is low. Such a treatment gap with respect to recommended practice⁽¹⁵⁾ has been observed in many other health systems.⁽¹⁶⁻²¹⁾

In France, densitometry has been fully reimbursed since 2006, is recommended in osteoporosis practice guidelines, and widely available. In fact, France has the highest number of densitometry machines per head of population in Europe. Similarly, osteoporosis treatments are fully reimbursed. The low numbers of patients experiencing fractures to whom densitometry is offered and treatments prescribed has been a consistent finding of studies in France for the last twenty years^(22,23). The reason for this possibly lies in the segmentation of care in France, such that when a patient is discharged from hospital after a fracture, there is little communication between the orthopedic surgery department and the general practitioner, who is responsible for prescribing densitometry and osteoporosis treatments⁽²⁴⁾. Establishment of more Fracture Liaison Services in France (there are currently only thirty) for osteoporosis care, which have been shown to be a cost-effective way to reduce refracture rates and their associated expenditure in other countries such as the United Kingdom^(25,26), may help improve this situation⁽²⁷⁾. The treatment gap in osteoporosis care in France is well recognized and has recently prompted initiatives on the part of the health authorities to improve this as part of the ‘*Ma santé 2022, un engagement collectif*’ programme.

A novel feature of our study was the longitudinal follow-up of costs. This demonstrated that, over five years, the fracture-related costs continued to dominate the economic burden of osteoporosis. In the years following the index fracture, acute fracture care cost around €900 a year on average compared to around €110 for osteoporosis management (which includes the costs of medication). This cost was principally incurred as a result of refractures. Osteoporosis management costs remained low and actually declined over the follow-up period.

It is well-established that osteoporotic fractures frequently cluster in time^(28,29) and that the risk of refracture can be reduced by specific osteoporotic treatment.⁽³⁰⁾ From a strictly economic standpoint, although more intensive osteoporosis management would involve additional expenditure outlay in the short term, it may be expected that, in theory, this would be compensated by important savings in the long-term due to prevention of costs associated with refracture. An increase in the proportion of patients actively managed for their osteoporosis, as well as more active management in terms of prescription of specific treatments and regular follow-up with densitometry would both be expected to reduce the economic burden of osteoporotic fractures. We cannot address this question directly since we do not have data on the relative risk of refracture in patients who were treated compared to untreated patients in this population. A dedicated cost-effectiveness study of osteoporosis treatment in the French context would be necessary. A recent modelling study has suggested that such a treatment paradigm would be cost-effective in several European countries, including France, although this was based on extrapolations from rather old data.⁽³¹⁾ Dedicated cost-effectiveness studies have been performed for certain of these treatments in other European countries, such as denosumab in Sweden⁽³²⁾, Spain⁽³³⁾, and Belgium⁽³⁴⁾ and zoledronic acid in Norway, Finland and the Netherlands⁽³⁵⁾; these have generally concluded that the treatments are cost-effective, particularly in high-risk patients. A study evaluating cost-effectiveness in France is currently underway.

We also performed a multivariate analysis of variables potentially influencing cost. Older age is associated with higher cost, which would be expected as these patients are more fragile, and certain fracture sites, notably the hip and pelvis, which are associated with reduced mobility, also carry a higher cost. Mobility impairment has also been identified in the ICUROS study as a predictor of increased costs.⁽¹⁴⁾ In addition to these unsurprising associations, a history of osteoporotic fracture is also associated with higher cost. This observation is consistent with the longitudinal data demonstrating that the high cost of osteoporosis is driven by repeated fracture events, and further emphasizes the importance of measures to reduce fracture risk in patients with osteoporosis.

The study has certain limitations, most of which are intrinsic to the nature of the database. All severe osteoporotic fractures may not have been captured, for example because fractures that

did not require hospitalization, such as certain vertebral and multiple rib fractures will not have been documented. In addition, around one-third of the ~500,000 patients originally identified were excluded from the analysis, principally because the site of the fracture could not be identified, because the patient had a confounding pathology which precluded definite attribution of the fracture to osteoporosis, or because the patient was not continuously insured during the follow-up period. It should also be noted that wrist and forearm fractures, which are not considered to be severe osteoporotic fractures in the French osteoporosis practice guidelines ⁽¹²⁾, were not evaluated, and the cost of these fractures are thus not included. Patients with fractures at multiple sites were also excluded. For these reasons, the cost estimates reported in the study are likely to underestimate the real total cost of these fractures. Moreover, the notion of a severe osteoporotic fracture is not specifically documented in the hospital discharge summary and the attribution of this diagnosis was made operationally by excluding patients with alternative explanations for fractures (such as Paget's disease or accidents). For this reason, certain cases of severe osteoporotic fracture may have been wrongly excluded, which may also contribute to an underestimate of the real burden of osteoporosis fracture. It is also not possible to identify consultations with specialists in hospital, so the proportion of patients consulting rheumatologists, which is only based on community-based physicians, is probably underestimated. In addition, we did not capture costs generated from consultations from other medical specialties such as gynecologists or geriatricians, who may also contribute to osteoporosis care, or costs that were not reimbursed, such as over-the-counter purchase of calcium or vitamin D supplements. Finally, the specific osteoporosis-related costs were estimated from expenditures considered *a priori* as likely to be associated with acute fracture care or osteoporosis management. However, the degree of imprecision is expected to be limited given that the management of osteoporosis and osteoporotic fractures is relatively specific. It should also be noted that the end of the follow-up period was in 2016, and it is possible that costs will have evolved since this time. However, we do not consider that structural changes in osteoporosis care in France have occurred since 2016, that would have a major impact on cost.

In conclusion, the FRACTOS study has shown that the cost of severe osteoporotic fractures to the French healthcare system is much higher than previously estimated in earlier insurance database studies. Over time, most of the long-term cost is associated with treatment of refractures, and a relatively low proportion of patients are treated for osteoporosis. Improved fracture prevention measures in patients with osteoporosis is crucial to reduce the economic burden of the disease.

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Author contributions

TT, FT, GB, AC, FM, LP, CC, CR and JP designed the study and developed the methodology. GB, FM and CC extracted the data from the SNDS database and performed the data analysis. TT, FT, CR and JP were responsible for data interpretation. All authors contributed to the development and revision of the manuscript and approved the final version of the manuscript. All authors take responsibility for their contributions as outlined above.

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1 **Tables**

2 **Table 1.** Healthcare resource utilization by fracture site over the twelve-month period after the index hospitalization

3

	Hip (N = 208,102)	Proximal humerus (N = 52,468)	Vertebra (N = 31,979)	Pelvis (N = 38,051)	Multiple ribs (N = 17,184)	TOTAL (N = 347,784)
Related to the fracture itself						
Hospitalization for severe osteoporotic fracture	208,102 (100%)	52,468 (100%)	31,979 (100%)	38,051 (100%)	17,184 (100%)	347,784 (100%)
Index hospitalization	208,102 (100%)	52,468 (100%)	31,979 (100%)	38,051 (100%)	17,184 (100%)	347,784 (100%)
Readmission	20,872 (10.0%)	5,290 (10.1%)	4,405 (13.8%)	4,972 (13.1%)	1,083 (6.3%)	36,622 (10.5%)
Follow-up and rehabilitation care	116,386 (55.9%)	15,577 (29.7%)	6,821 (21.3%)	20,409 (53.6%)	2,127 (12.4%)	161,320 (46.4%)
Home care	851 (0.4%)	80 (0.2%)	94 (0.3%)	152 (0.4%)	6 (<0.1%)	1,183 (0.3%)
Surgeon visit ¹	63,110 (30.3%)	18,526 (35.3%)	5,421 (17.0%)	6,290 (16.5%)	1,397 (8.1%)	94,744 (27.2%)
Outpatient physiotherapy session ²	100,262 (48.2%)	37,054 (70.6%)	13,199 (41.3%)	14,519 (38.2%)	3,333 (19.4%)	168,367 (48.4%)
Number of sessions per patient (mean ± SD)	8.5 ± 12.7	13.9 ± 13.5	5.5 ± 9.4	5.8 ± 10.6	2.5 ± 6.7	8.5 ± 12.4
Median [IQR]	0 [0-14]	12 [0-22]	0 [0-9]	0 [0-9]	0 [0-0]	0 [0-15]
X-ray sessions ³	188,313 (90.5%)	47,978 (91.4%)	25,190 (78.8%)	30,116 (79.1%)	12,624 (73.5%)	304,221 (87.5%)
Medical devices	9,640 (4.6%)	842 (1.6%)	622 (1.9%)	1,168 (3.1%)	244 (1.4%)	12,516 (3.6%)
Related to management of osteoporosis						
Community rheumatologist consultation	12,539 (6.0%)	4,357 (8.3%)	4,420 (13.8%)	3,662 (9.6%)	1,335 (7.8%)	26,313 (7.6%)

	Hip (N = 208,102)	Proximal humerus (N = 52,468)	Vertebra (N = 31,979)	Pelvis (N = 38,051)	Multiple ribs (N = 17,184)	TOTAL (N = 347,784)
GP consultation for prescription of an osteoporosis treatment	79,989 (38.4%)	21,127 (40.3%)	14,412 (45.1%)	18,179 (47.8%)	4,859 (28.3%)	138,566 (39.8%)
Dentist visit	42,079 (20.2%)	15,375 (29.3%)	11,626 (35.4%)	10,301 (27.1%)	5,497 (32.0%)	84,878 (24.4%)
Bone densitometry	8,851 (4.3%)	2,938 (5.6%)	4,137 (12.9%)	2,117 (5.6%)	431 (2.5%)	18,474 (5.3%)
Blood tests	155,971 (74.9%)	40,117 (76.5%)	24,324 (76.1%)	29,290 (77.0%)	12,590 (73.3%)	262,310 (75.4%)
Specific osteoporosis medication delivered during year	31,385 (15.1%)	8,127 (15.5%)	8,250 (25.8%)	8,683 (22.8%)	1,775 (10.3%)	58,220 (16.7%)

4 Data are provided for the 356,895 patients of the analysis population. Unless otherwise specified, data are presented as the number (%) of patients using each healthcare resource item during
5 the twelve months following the index hospitalization. Definition of items as in Supplementary Table 2.

6 ¹Within the two months following the index hospitalization for a severe osteoporotic fracture. ²Within the three months following the index hospitalization for a severe osteoporotic fracture.

7 ³Within the twelve months following the index hospitalization for a severe osteoporotic fracture.

8 IQR: interquartile range; SD: standard deviation.

9

10 **Table 2.** Mean and median costs of patients hospitalized for severe osteoporotic fractures (2018 €)

11

	Hip	Proximal humerus	Vertebra	Pelvis	Multiple ribs	TOTAL
	(N = 215,672)	(N = 52,922)	(N = 32,231)	(N = 38,620)	(N = 17,450)	(N = 356,895)
Year 1: annual per capita costs						
Total cost -						
Mean ±SD	21,085 ± 17,740	12,559 ± 17,313	12,935 ± 15,600	17,074 ± 17,284	8,598 ± 10,090	18,040 ± 17,653
Median [IQR]	16,342 [9,283-27,339]	6,731 [2,727-16,263]	7,895 [3,573-16,077]	12,044 [5,370-22,649]	4,968 [1,745-10,992]	13,038 [6,056-24,054]
Related to the fracture itself						
Mean ± SD	20,964 ± 17,750	12,423 ± 17,319	12,723 ± 15,600	16,921 ± 17,291	8,474 ± 10,922	17,905 ± 17,664
Median [IQR]	16,207 [9,157-27,219]	6,591 [2,570-16,122]	7,682 [3,359-15,824]	11,860 [5,220-22,525]	4,852 [1,597-10,873]	12,901 [5,904-23,921]
Related to osteoporosis management						
Mean ± SD	122 ± 218	136 ± 196	213 ± 463	153 ± 309	125 ± 182	135 ± 258
Median [IQR]	65 [14-154]	88 [34-173]	108 [46-225]	80 [26-184]	85 [33-158]	75 [20-167]
Years 2 – 5: annual per capita costs						
Total cost -						
Mean ± SD	933 ± 3,356	814 ± 3,006	724 ± 2,972	1,152 ± 3,900	637 ± 2,817	901 ± 3,307
Median [IQR]	67 [16-214]	82 [31-198]	88 [36-215]	82 [26-256]	71 [28-154]	74 [22-210]

	Hip (N = 215,672)	Proximal humerus (N = 52,922)	Vertebra (N = 32,231)	Pelvis (N = 38,620)	Multiple ribs (N = 17,450)	TOTAL (N = 356,895)
Related to the fracture itself ¹						
Mean ± SD	845 ± 3,348	716 ± 2,999	595 ± 2,955	1,048 ± 3,886	550 ± 2,811	806 ± 3,298
Median [IQR]	0 [0-22]	0 [0-19]	0 [0-18]	0 [0-26]	0 [0-13]	0 [0-20]
Related to osteoporosis management						
Mean ± SD	88 ± 165	98 ± 157	129 ± 225	105 ± 225	87 ± 126	96 ± 177
Median [IQR]	43 [11-108]	60 [22-122]	70 [29-143]	55 [18-125]	57 [22-109]	50 [15-116]

12 Data are provided for the 347,784 patients of the analysis population who completed 12 months of follow-up.

13 ¹Including both costs of refracture events and of complications of the initial fracture

14 IQR: interquartile range; SD: standard deviation.

15

16

17 **Table 3.** Mean *per capita* costs of specific healthcare consumption (Year 1)

18

Item	Mean <i>per capita</i> cost (2018 €)		
	Men (N = 91,137)	Women (N = 265,758)	Total (N = 356,895)
Related to the fracture itself	16,836 ± 17,690		17,905 ± 17,664

Mean ± SD	11,330 [4,697- 22,777]	18,271 ± 17,640	12,901 [5,904 – 23,921]
Median [IQR]		13,433 [6,426 – 24,284]	
Hospitalization	11,017 (65.4%)	10,733 (58.7%)	10,806 (60.3%)
Follow-up and rehabilitation care	5,499 (32.7%)	7,171 (39.2%)	6,744 (37.7%)
Home care	43 (0.3%)	34 (0.2%)	36 (0.2%)
Surgeon visits	3 (<0.1%)	3 (<0.1%)	3 (<0.1%)-
Outpatient physiotherapy sessions	93 (0.6%)	134 (0.7%)	124 (0.7%)
X-ray sessions	30 (0.2%)	38 (0.2%)	36 (0.2%)
Medical devices	27 (0.2%)	26 (0.1%)	26 (0.1%)
Transportation for any of the above	125 (0.7%)	133 (0.7%)	131 (0.7%)
Related to management of osteoporosis		146 ± 275	
Mean ± SD	106 ± 198	79 [22 – 181]	135 ± 258
Median [IQR]	66 [15 – 134]		75 [20 – 167]
Community rheumatologist consultation	1 (0.9%)	2 (1.4%)	2 (1.5%)
GP visit for osteoporosis medication	54 (50.9%)	49 (33.6%)	50 (37.0%)
Dentist visit	1 (0.9%)	1 (0.7%)	1 (0.7%)
Bone densitometry	<1 (0.4%)	1 (0.7%)	1 (0.7%)

Blood tests	29 (27.4%)	36 (24.7%)	34 (25.2%)
Osteoporosis medication	12 (11.3%)	49 (33.6%)	39 (28.9%)
Transportation for any of the above	8 (7.5%)	8 (5.5%)	8 (5.9%)

19 Data are provided for the 356,895 patients of the analysis population. Data are presented as mean € ± SD and Median € (IQR) for the per capita costs at year 1 for the global
20 costs related to the fracture itself and to management of osteoporosis. For sub-divisions of these costs, data are presented as mean per capita cost in € and the percentage of the
21 global cost it accounted for.
22

23 **Figure Legends**

24

25 **Figure 1.** Patient flow-chart

26 ¹Reasons for non-eligibility are not mutually exclusive and individual patients may thus have
27 more than one reason for exclusion. A total of 203,604 patients were not eligible for the study.
28 The sum of the number of individual patients with a specific reason for exclusion
29 (confounding pathology for 98,525 patients, <50 years of age for 51,716 patients, *et caetera*
30 as listed in the right-hand column) is 212,715 patients. In consequence, 9,111 patients
31 (212,715 minus 203,604) present more than one reason for non-eligibility.

32 ²History of Paget's disease, cancer, infectious arthritis, or bone fragility secondary to
33 malignant disease or to surgical interventions.

34 ³Covered by more than one Health Insurance Regimen during the study period.

35 Percentages are calculated with respect to the preceding line.

36

37 **Figure 2.** Variation of fracture-related rehospitalization and osteoporosis management rates
38 over time.

39

40 **Figure 3.** Treatment persistence with first-line specific osteoporosis treatments

41

42 **Figure 4.** Variation of cost of osteoporosis over time.

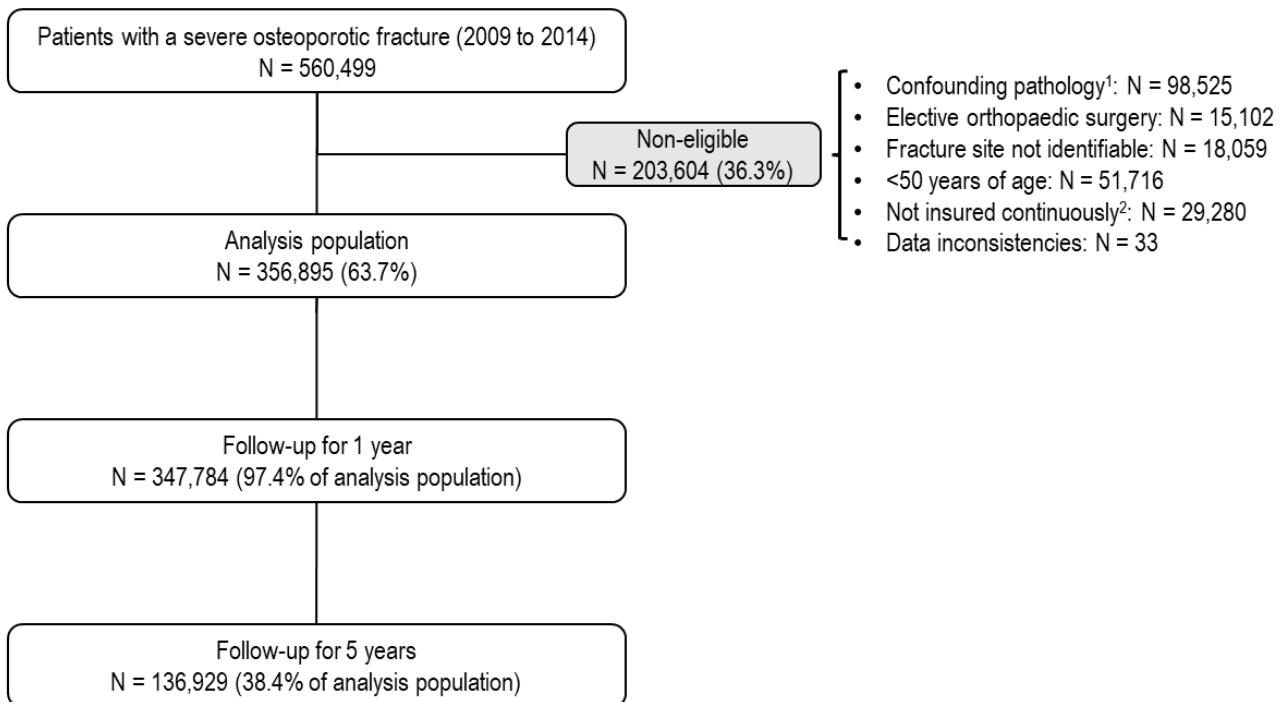
43 Costs (Y-axis) are presented on a logarithmic scale for clarity, due to the large variation in the
44 different costs presented.

45

46 **Figure 5.** Variables associated with the mean *per capita* cost of osteoporosis over the five-
47 year period

48

49 **Figure 1. Patient flow-chart**



51 ¹Reasons for non-eligibility are not mutually exclusive and individual patients may thus have more than one reason for
 52 exclusion. A total of 203,604 patients were not eligible for the study. The sum of the number of individual patients with a
 53 specific reason for exclusion (confounding pathology for 98,525 patients, <50 years of age for 51,716 patients, et caetera as
 54 listed in the right-hand column) is 212,715 patients. In consequence, 9,111 patients (212,715 minus 203,604) present more
 55 than one reason for non-eligibility.

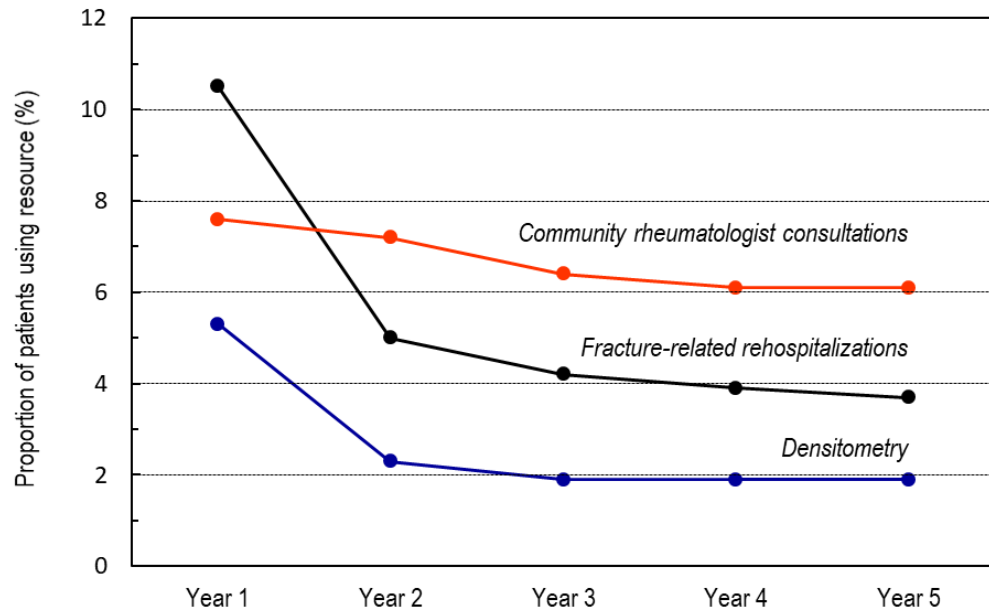
56 ²History of Paget's disease, cancer, infectious arthritis, or bone fragility secondary to malignant disease or to surgical
 57 interventions.

58 ³Covered by more than one Health Insurance Regimen during the study period.

59 Percentages are calculated with respect to the preceding line.

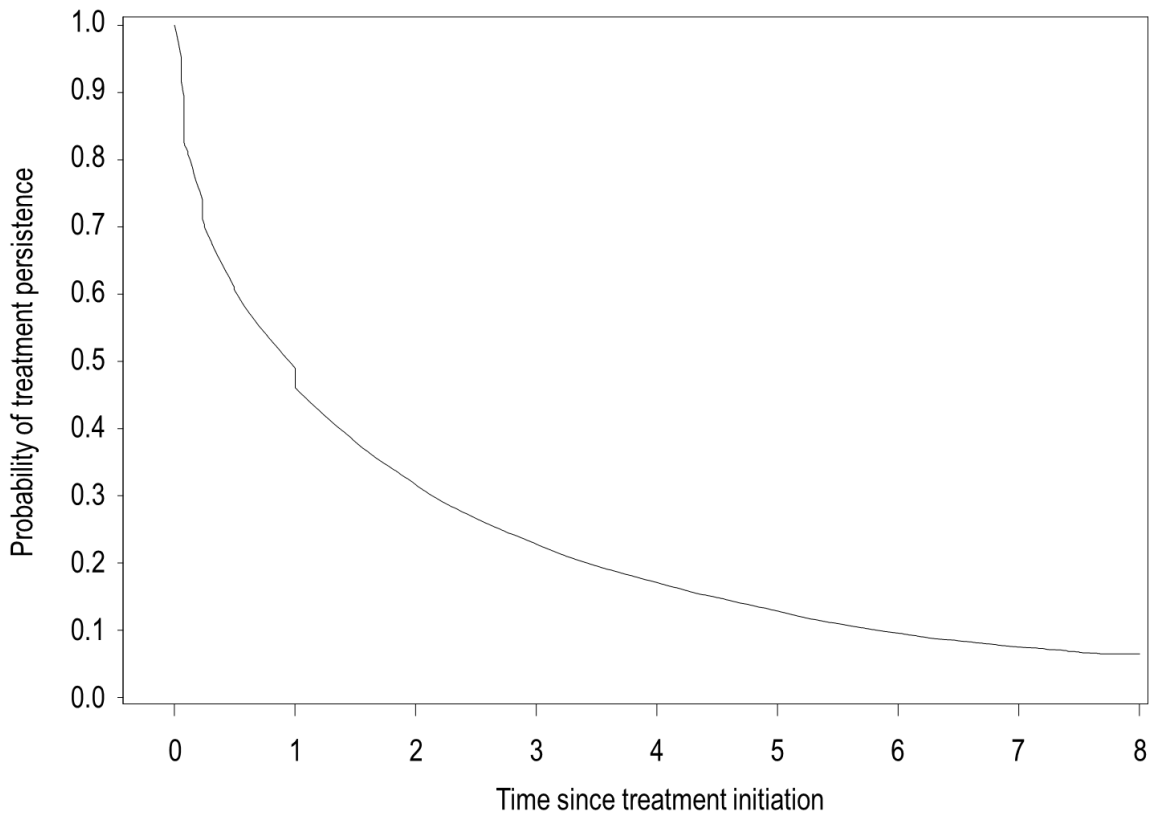
60

62 **Figure 2.** Variation of fracture-related rehospitalization and osteoporosis management rates
63 over time.



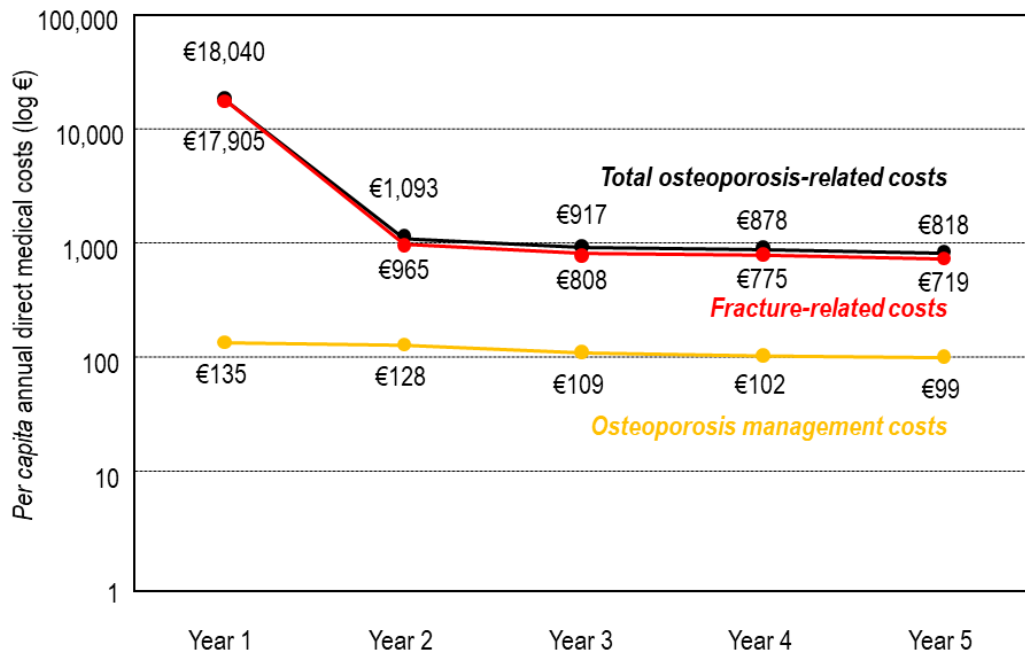
64

65 **Figure 3.** Treatment persistence with first-line specific osteoporosis treatments



66

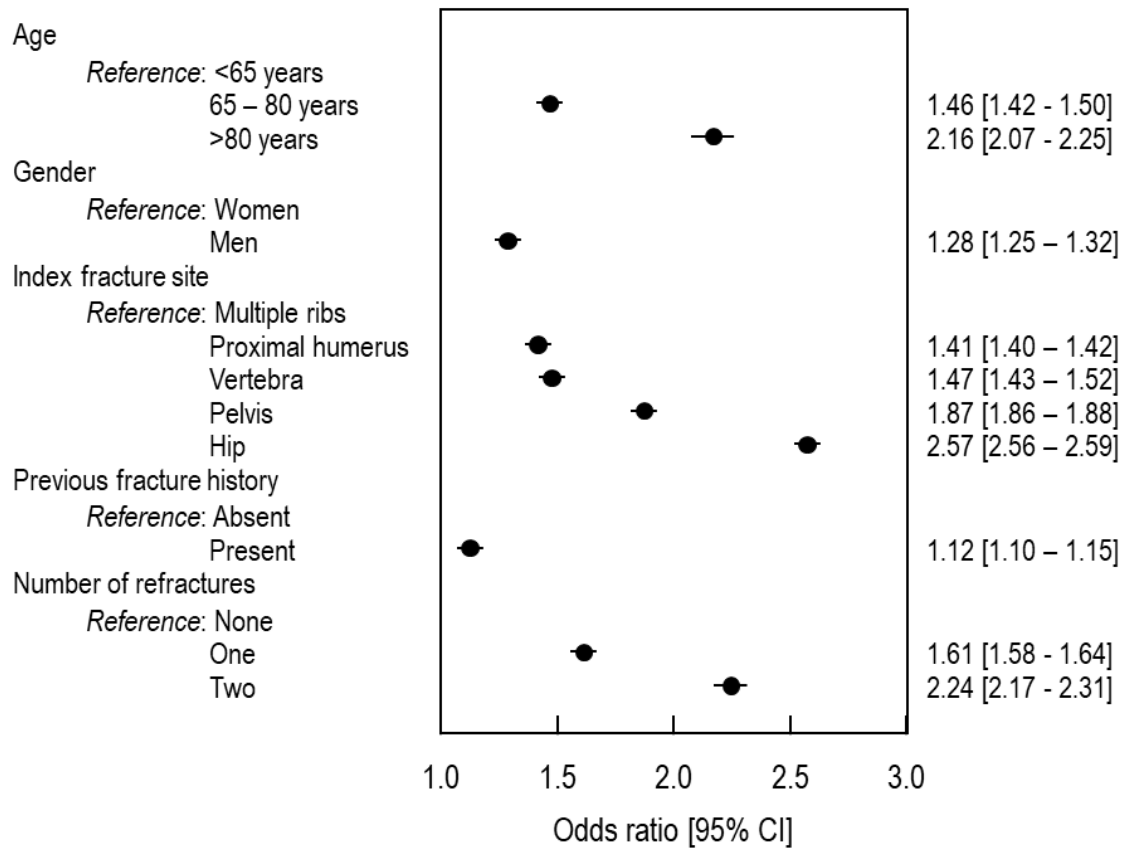
67 **Figure 4.** Variation of cost of osteoporosis over time.



68

69 *Costs (Y-axis) are presented on a logarithmic scale for clarity, due to the large variation in*
70 *the different costs presented.*

71 **Figure 5.** Variables associated with the mean *per capita* cost of osteoporosis over the five-
 72 year period



73