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Osteoporosis: burden, health care provision and opportunities in the EU

A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA)

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Abstract

Osteoporosis, literally "porous bone", is a disease characterized by weak bone. It is a major public health problem, affecting hundreds of millions of people worldwide, predominantly postmenopausal women. The main clinical consequence of the disease is bone fractures. It is estimated that one in three women and one in five men over the age of fifty worldwide will sustain an osteoporotic fracture. Hip and spine fractures are the two most serious fracture types, associated with substantial pain and suffering, disability, and even death. As a result, osteoporosis imposes a significant burden on both the individual and society. During the past two decades, a range of medications has become available for the treatment and prevention of osteoporosis. The primary aim of pharmacological therapy is to reduce the risk of osteoporotic fractures.

The objective of this report is to review and describe the current burden of osteoporosis and highlight recent advances and ongoing challenges for treatment and prevention of the disease. The report encompasses both epidemiological and health economic aspects of osteoporosis and osteoporotic fractures with a primary geographic focus on France, Germany, Italy, Spain, Sweden, and the UK. Projections of the future prevalence of osteoporosis and fracture incidence, the total societal burden of the disease, and the consequences of different intervention strategies receive special attention. The report may serve as a basis for the formulation of healthcare policy concerning osteoporosis in general and the treatment and prevention of osteoporosis in

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particular. It may also provide guidance regarding the overall healthcare priority of the disease.

The report is divided into six chapters:

1. Introduction to osteoporosis

The first chapter provides a brief review of osteoporosis, how osteoporotic fractures are defined, a description of the most common osteoporotic fractures, the burden of fractures, as well as challenges in the delivery of health care to reduce the number of fractures.

2. Medical innovation and clinical progress in management of osteoporosis

The second chapter reviews the measurement of bone mineral density, diagnosis of osteoporosis, methods for assessment of fracture risk, the development of interventions that reduce the risk of fractures, practice guidelines, and the cost-effectiveness of osteoporosis treatments.

3. Epidemiology of osteoporosis

The third chapter reviews the epidemiology and consequences of osteoporosis and fractures, as well as different approaches for setting intervention thresholds (i.e. at what fracture risk it is appropriate to initiate treatment).

4. Burden of osteoporosis

The fourth chapter presents a model estimation of the current burden of osteoporosis in the five largest countries in the European Union (EU5) and Sweden. The burden is described in terms of fractures, costs, and quality-adjusted life years (QALYs) lost.

5. Uptake of osteoporosis treatments

The fifth chapter provides a description of the current uptake of osteoporosis treatments, that is, how many patients of those eligible for treatment that actually can be treated in France, Germany, Italy, Spain, Sweden and the UK. International sales data from 1998 and forward was used to analyse international variations in treatment uptake.

6. The future burden of fractures and the consequences of increasing treatment uptake

The last chapter presents projections of how the demographic changes in the five largest countries in the France, Germany, Italy, Spain, Sweden and the UK will impact the burden of osteoporosis up to 2025. Hypothetical projections of increments in treatment provision are also explored, and the impact of increased treatment on costs, fracture rates, and morbidity is estimated.

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List of abbreviations

ALN	Alendronate
AOPS	Alendronate osteoporosis prevention study
ATC	Anatomical therapeutic classification
BMD	Bone mineral density
BMI	Body mass index
BPH	Benign prostatic hyperplasia
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRF	Clinical risk factor
DALY	Disability-adjusted life year
DDD	Defined daily dosage
DXA	Dual-energy x-ray absorptiometry
EFPIA	European Federation of Pharmaceutical Industry Associations
EMA	European Medicines Agency
EPIC	European prospective investigation into cancer and nutrition
EPOS	European prospective osteoporosis study
EU5	Refers to 5 countries of the European Union (France, Germany, Italy, Spain and the UK)
EU5+	EU5 with the inclusion of Sweden
FRAX®	WHO Fracture risk assessment tool
GDP	Gross domestic product
GIOP	Glucocorticoid-induced osteoporosis
GPRD	General practice research database
GRIO	Groupe de Recherche et d'Informations sur les Ostéoporoses
HAS	Haute Autorité de Santé
HRT	Hormone replacement therapy
ICD	International classification of diseases
IHD	Ischemic heart disease
IMS	Intercontinental Marketing Services
INSEE	Institut National de la Statistique et des Etudes Economiques
IOF	International Osteoporosis Foundation
MEDOS	Mediterranean osteoporosis study
mg	Milligram
MPR	Medication possession ratio
MS	Multiple sclerosis
NFkB	Nuclear factor kappa B
NHANES	National health and nutrition examination survey
NICE	National Institute of Health and Clinical Excellence
NOGG	National Osteoporosis Guideline Group
OA	Osteoarthritis
OPG	Osteoprotegerin
PMSI	Programme de médicalisation des systèmes d'information
POSSIBLE EU	Prospective observational study investigating bone loss experience in Europe
PPV	Positive predicted value
pQCT	Peripheral quantitative computed tomography
PTH	Parathyroid hormone
QALY	Quality-adjusted life year
QCT	Quantitative computed tomography
QoL	Quality of life
QUS	Quantitative ultrasound
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCP	Royal College of Physicians
RCT	Randomized clinical trial
RR	Risk ratio
SARA	Swedish adherence register analysis
SD	Standard deviation
SERM	Selective estrogen receptor modulator
T-score	The deviation in units of SD of a BMD value from the mean value in premenopausal women
WHO	World Health Organization
WTP	Willingness to pay

1 Introduction to osteoporosis

Summary

This introductory chapter briefly reviews the way in which osteoporotic fractures are defined, describes the most common osteoporotic fractures, the extent of the burden world wide shown in current literature and the challenges faced in the delivery of health care to reduce the number of fractures.

The key messages of this chapter are:

Osteoporosis is characterized by reduced bone mass and disruption of bone architecture, resulting in increased bone fragility and increased fracture risk.

The definition of osteoporotic fractures is not straightforward, but is generally based on the concepts of "low energy impact", fragility and age.

The approach used in this report, as elsewhere, was to characterize fracture sites as osteoporotic when they are associated with low bone mass and their incidence rises with age after the age of 50 years.

The most common osteoporotic fractures defined in this way are those at the hip, spine, forearm, and humerus.

There are large variations in the incidence of osteoporotic fractures between and within countries.

Risk factors for osteoporosis and osteoporotic fractures include a low body mass index, low calcium intake, reduced sunlight exposure and early menopause.

Osteoporosis causes more than 8.9 million fractures annually worldwide and over one third of all osteoporotic fractures occur in Europe.

In Europe osteoporotic fractures account for 2 million disability-adjusted life years (DALYs) annually, somewhat more than accounted for by hypertensive heart disease and rheumatoid arthritis, respectively.

The frequency of osteoporotic fracture is rising in many countries. Reasons for this relate in part to the increased longevity of the population.

Despite advances in the diagnosis, assessment and treatment of osteoporosis, a minority of patients at high fracture risk is identified for treatment.

The assessment of best practices in prevention and treatment and the adoption of these across countries can potentially result in significant reductions in the burden of osteoporosis.

1.1 Introduction

Osteoporosis is characterized by reduced bone mass and disruption of bone architecture, resulting in increased bone fragility and increased fracture risk [1]. Although the disease has been documented for many years, osteoporosis and the fractures that arise were commonly viewed as inevitable consequences of the aging process. Indeed, the conceptual description of osteoporosis that is now widely accepted was formulated less than 20 years ago [1]. The publication of a World Health Organization (WHO) report on the assessment of fracture risk and its application to screening for postmenopausal osteoporosis in 1994 provided diagnostic criteria for osteoporosis based on the measurement of bone mineral density (BMD) and recognized osteoporosis as an established and well-defined disease that affected more than 75 million people in the United States, Europe and Japan [2].

The focus of this report is on differences in access to treatments for osteoporosis, describing the size of the problem using a diverse set of metrics, and the treatments available and their uptake. This forms the basis for an analysis to identify causes and consequences of variations in access and for actions needed to improve standards of care today and in the future, with the aim of reducing the burden of the disease.

The consequences of osteoporosis reside in the fractures that arise. This introduction reviews briefly the way in which osteoporotic fractures are defined, describes the most common osteoporotic fractures, the extent of the burden worldwide shown in current literature and the challenges faced in the delivery of health care to reduce the number of fractures.

1.2 Defining an osteoporotic fracture

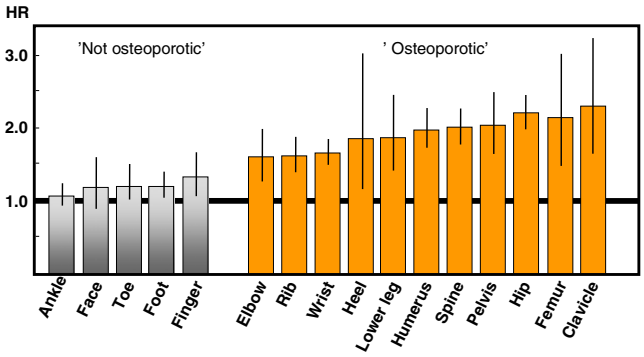
Osteoporosis is manifested by fractures but the definition of an osteoporotic fracture is not straightforward. Opinions differ concerning the inclusion or exclusion of different sites of fracture in describing osteoporotic fractures. One approach is to consider all fractures from low energy trauma as being osteoporotic. "Low energy" may variously be defined as a fall from a standing height or less, or trauma that in a healthy individual would not give rise to fracture [3]. This characterization of low trauma indicates that the vast majority of hip and forearm fractures are low energy injuries or fragility fractures. At the age of 50 years, approximately 75% of people hospitalized for vertebral fractures have fractures that are attributable to low energy injuries, increasing to 100% by the age of 90 years [4]. The consideration of low energy has the merit of recognizing the multifactorial causation of fracture, but osteoporotic

individuals are more likely to fracture than their normal counterparts following high energy injuries [5]. As might be expected, there is also an imperfect concordance between low energy fractures and those associated with reductions in BMD [6, 7].

The rising incidence of fractures with age does not provide direct evidence for osteoporosis, since a rising incidence of falls could also be a cause. By contrast, a lack of increasing incidence with age is reasonable presumptive evidence that a fracture type is unlikely to be osteoporosis-related. An indirect arbiter of an osteoporotic fracture is the finding of a strong association between the fracture and the risk of classical osteoporotic fractures at other sites. Vertebral fractures, for example, are a very strong risk factor for subsequent hip and vertebral fracture [8–11] whereas forearm fractures predict future vertebral and hip fractures [12].

Due to the difficulties of knowing which fractures have been caused by low energy trauma, the approach used in this report and elsewhere was to characterize fracture sites as osteoporotic when they are associated with low bone mass and their incidence rises with age after the age of 50 years [13]. The most common fractures defined in this way are those at the hip, spine and forearm, and humerus but many other fractures after the age of 50 years are related at least in part to low BMD and should be regarded as osteoporotic [6, 14, 15]. These include fractures of the ribs, tibia (in women, but not including ankle fractures), pelvis and other femoral fractures (Fig. 1). Their neglect underestimates the burden of osteoporosis, particularly in younger individuals. Under this schema, the fracture sites that would be excluded include those at the ankle, hands and feet, digits, skull and face, and kneecap.

Fig. 1 Hazard ratio and 95% confidence intervals for osteoporosis as judged by BMD at the hip according to fracture site in women from France [15]



1.3 Common osteoporotic fractures

The most common osteoporotic fractures comprise vertebral compression fractures, fractures at the forearm (particularly Colles' fracture), hip fractures, and proximal humerus fractures [2]. In Sweden, the remaining lifetime risk at the age of 50 years of sustaining a hip fracture is 22.9% in women and 10.7% in men. The remaining lifetime risk of a major osteoporotic fracture (clinical spine, hip, forearm or humeral fracture) is 46.4% in women and 22.4% in men [16] (Table 1). The vast majority of osteoporotic fractures occur in elderly women [17]. Overall, women have about twice as high a risk of sustaining any fracture than men. However, there are variations between different fracture sites. For example women have about a 5 times higher risk of sustaining a forearm fracture than men but less than twice the risk of sustaining a spine fracture. The reasons for this relate in part to differences in bone density at maturity and in particular to the loss of bone that occurs after the menopause. In addition, women live longer than men and are exposed, therefore, for longer periods to a reduced bone density and other risk factors for osteoporosis or fracture. Men have higher rates of fracture-related mortality than women [18], possibly related to higher rates of co-morbidity.

Table 1 Remaining lifetime probability of fracture (%) in men and women from Sweden at the ages shown [16]. The risk ratio refers to the female/male probabilities

	At 50 years			At 80 years		
Type of fracture	Men	Women	Risk ratio	Men	Women	Risk ratio
Forearm	4.6	20.8	4.5	1.6	8.9	5.6
Hip	10.7	22.9	2.1	9.1	19.3	2.1
Spine [a]	8.3	15.1	1.8	4.7	8.7	1.9
Proximal humerus	4.1	12.9	3.1	2.5	7.7	3.1
Any of these	22.4	46.4	2.1	15.3	31.7	2.1

[a]Clinical spine fracture

The incidence of fragility fractures increases markedly with age, though the rate of rise with age differs for different fracture outcomes. For this reason, the proportion of fractures at any site also varies with age. This is most evident for forearm and hip fractures [19] (Fig. 2). Thus forearm fractures account for a greater proportion at younger ages than in the elderly. Conversely, hip fractures are rare at the age of 50 years but become the predominant osteoporotic fracture from the age of 75 years. In women, the median age for distal forearm fractures is around 65 years and for hip fracture, 80 years. Thus both the number of fractures and the type of fracture are critically dependent on the age of the populations at risk. The most frequent fractures are those at the hip, spine and distal forearm (Fig. 3), in women these account for the majority of fractures after the age of 50 years.

Fig. 2 The site specific pattern of osteoporotic fractures by age worldwide [19]

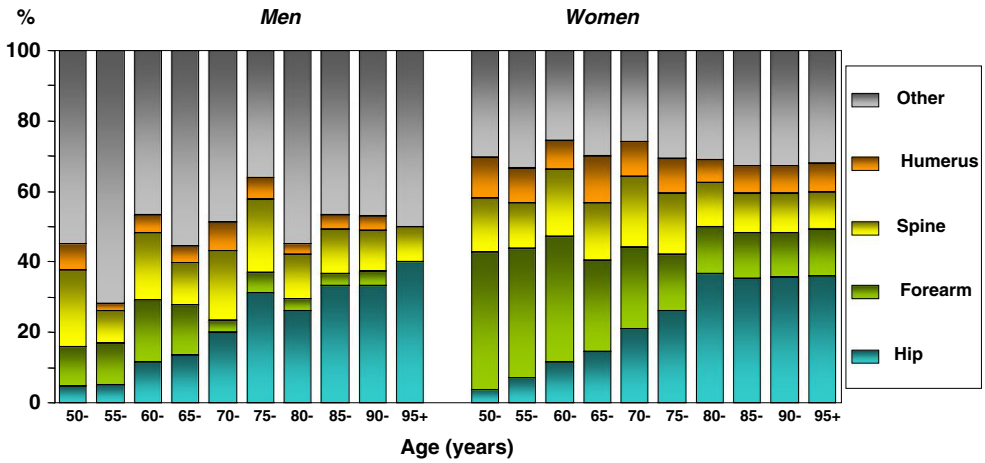
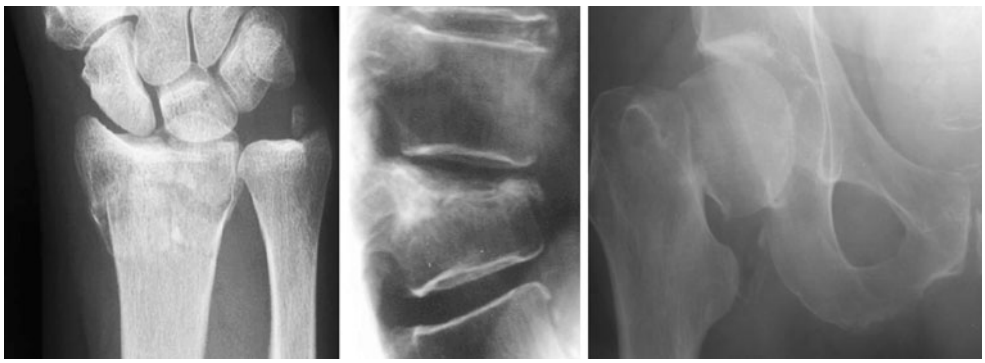


Fig. 3 Typical osteoporotic fractures at the distal forearm (left), spine (centre) and hip (right)



1.3.1 Hip fracture

Hip fracture is the most serious osteoporotic fracture. Most are caused by a fall from the standing position, although they sometimes occur spontaneously [20]. The risk of falling increases with age and is somewhat higher in elderly women than in elderly men. About one third of elderly individuals fall annually, and 5% will sustain a fracture and 1% will suffer a hip fracture [21]. Hip fracture is painful and nearly always necessitates hospitalization.

A hip fracture is a fracture of the proximal femur, either through the femoral cervix (sub-capital or trans-cervical: intra-capsular fracture – as in Fig. 3) or more distally through the trochanteric region (intra-trochanteric: extra-capsular fracture). Trochanteric fractures are more characteristically osteoporotic, and the increase in age-specific and sex-specific risks for hip fracture is greater for trochanteric than for cervical fractures [22]. Trochanteric fractures are also more commonly associated with a prior fragility fracture.

Displaced cervical fractures have a high incidence of malunion and osteonecrosis following internal fixation, and the prognosis is improved with hip replacement. Trochanteric hip fractures appear to heal normally after adequate surgical management. Complications may arise because of immobility. The outcome is much poorer where surgery is delayed for more than 3 days. Up to 20% of patients die in the first year following hip fracture, mostly as a result of serious underlying medical conditions [23, 24] and less than half of survivors regain the level of function that they had prior to the hip fracture [25]. Patients with hip fracture often have significant co-morbidities, so that not all deaths associated with hip fracture are due to the hip fracture event. It is estimated that approximately 30% of deaths are causally related [26]. When this is taken into account, hip fracture causes more deaths than road traffic accidents in Sweden and about the same number as those caused by breast cancer (Table 2).

Table 2 Causes of death in men and women aged 45 years or more from Sweden [26]

	Men	Women	Total	Share of all deaths (%)
Acute myocardial infarction	7,113	5,335	12,449	13
Lung cancer	1,761	1,112	2,873	3
Prostate cancer	2,480	0	2,480	3
Breast cancer	11	1,549	1,560	2
Hip fracture	566	854	1,420	2
Transport accident	422	142	564	1

1.3.2 Vertebral fracture

Falls account for only about one-third of new clinical vertebral fractures, and most are associated instead with other activities such as lifting or changing position. The vast majority of vertebral fractures are a result of moderate or minimal trauma [27]. The incidence and morbidity from vertebral fractures is not well documented, in part related to the difficulties in defining vertebral fracture, and because of the non-specific nature of the morbidity occasioned by the disorder (e.g., back pain). In addition, the diagnosis is made on a change in the shape of the vertebral body on x-rays. The deformities that result from osteoporotic fracture are usually classified as a crush fracture (involving compression of the entire vertebral body), a wedge fracture (in which there is anterior or posterior height loss), and biconcavity (where there is relative maintenance of the anterior and posterior heights with central compression of the end-plate regions). A number of morphometric approaches has been developed to quantify the shape of the vertebral body from radiographs of the lateral spine, and this has helped in defining the prevalence and incidence of vertebral fracture. A widely used clinical system is to classify vertebral fractures as mild (20%–25% height loss), moderate (25%–40% height loss), or severe (>40% height loss) [28].

A further problem in describing the epidemiology of vertebral fracture is that not all fractures come to clinical attention [29–31]. Estimates for the proportion of vertebral deformities that reach primary care attention vary, however, in different countries [29, 32, 33]. In register studies, the discharge rate for hospitalised vertebral fractures is closely correlated with the discharge rate for hip fracture [31]. In Sweden, approximately 23% of vertebral deformities come to clinical attention in women, and a somewhat higher proportion in men [33]. A similar proportion has been observed in the placebo wing of multinational intervention studies [34].

Vertebral fractures may give rise to pain, loss of height and progressive curvature of the spine (kyphosis). The consequences of kyphosis include difficulties in performing daily activities and a loss of self-esteem due to the change in body shape. Severe kyphosis also gives rise to respiratory and gastrointestinal disorders. Although vertebral fractures that come to clinical attention are less costly than hip fractures, the morbidity from an acute fracture in the first year is as severe as that due to a hip fracture [35], and is associated with an increase in mortality [36]. They are also a very strong risk factor for a further fracture at the spine and elsewhere [11].

1.3.3 Distal forearm fracture

The most common distal forearm fracture is a Colles' fracture. This fracture lies within 2.5 cm of the wrist joint margin and is associated with dorsal angulation and displacement of the distal fragment of the radius. It may be accompanied by a fracture of the ulna styloid process. A Smith fracture resulting in ventral angulation usually follows a forcible flexion injury to the wrist and is relatively uncommon in the elderly.

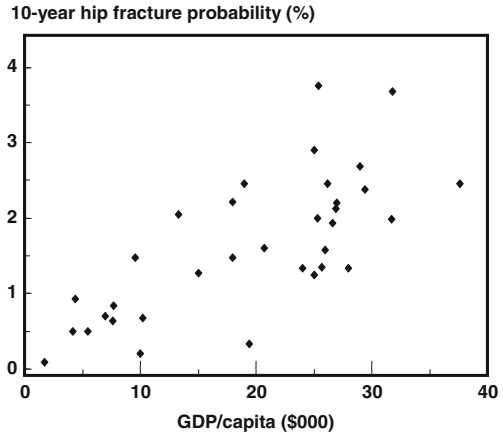
The cause of fracture is usually a fall on the outstretched hand [27]. Although fractures of the forearm cause less morbidity than hip fractures, are rarely fatal, and seldom require hospitalization, the consequences are often underestimated. Fractures are painful and need 4–6 weeks in plaster. Approximately 1% of patients with a forearm fracture become dependent as a result of the fracture [37], but nearly half report only fair or poor functional outcome at 6 months [38]. There is a high incidence of algodystrophy – a syndrome which gives rise to pain, tenderness, stiffness and swelling of the hand, and more rarely to frozen shoulder syndrome [39]. Moreover, the risk of other osteoporotic fractures in later life is also increased after Colles' fracture [11].

1.4 Fracture burden worldwide

There is a marked difference in the incidence of hip fracture worldwide and probably in other osteoporotic fractures. Indeed, the difference in incidence between countries is much greater than the differences in incidence between sexes within a country [40, 41]. Many risk factors for osteoporosis, and in particular for hip fracture have been identified which include a low body mass index, low calcium intake, reduced sunlight exposure and early menopause. These may have important effects within communities but do not explain differences in risk between communities. The factor which best predicts this is socio-

economic prosperity that in turn may be related to low levels of physical activity [42] (Fig. 4). This is plausible, but only a hypothesis. It will be important to determine whether this and other factors are truly responsible for the heterogeneity of fracture risk. If such factors can be identified and are reversible, the primordial prevention of hip fracture in those communities with presently low rates might be feasible.

Fig. 4 Correlation between average 10-year hip fracture probability in different countries and gross domestic product (GDP) per capita [42]



Osteoporosis causes more than 8.9 million fractures annually worldwide (Table 3) – approximately 1,000 per hour [19]. Fracture rates are higher in the western world than in other regions so that, despite the lower population, slightly more than one-third of all osteoporotic fractures occur in Europe.

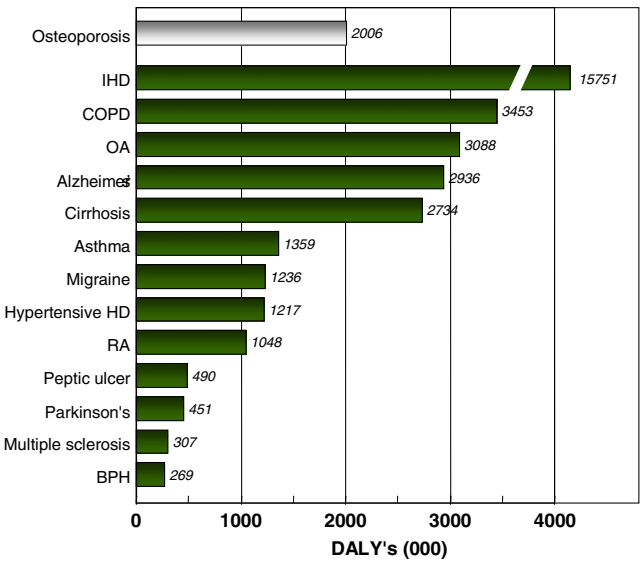
Table 3 Estimated number of osteoporotic fractures by site, in men and women aged 50 years or more in 2000, by WHO region [19]

	Number of fractures by site (in thousands)				All osteoporotic fractures	
WHO region	Hip	Spine	Proximal Humerus	Forearm	Number	%
Africa	8	12	6	16	75	0.8
Americas	311	214	111	248	1,406	15.7
South-East Asia	221	253	121	306	1,562	17.4
Europe	620	490	250	574	3,119	34.8
Eastern Mediterranean	35	43	21	52	261	2.9
Western Pacific[a]	432	405	197	464	2,536	28.6

[a] Includes Australia, China, Japan, New Zealand and the Republic of Korea

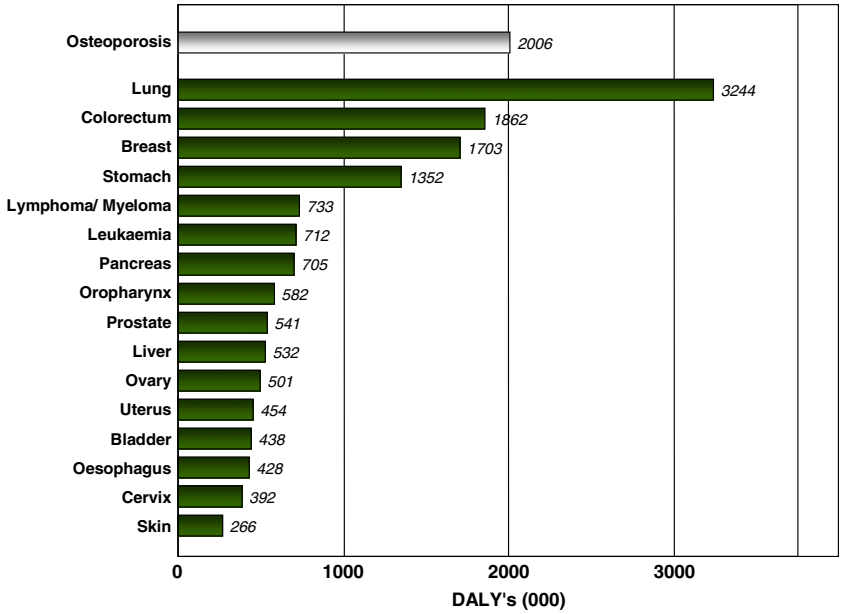
The global burden of osteoporosis can be quantified by disability adjusted life years (DALYs) [43]. This integrates the years of life lost due to a fracture and the disability in those that survive. A year lost due to premature mortality is equal to one DALY. If the quality of life is halved by a fracture (1 = death; 0 = perfect health), then a year of life disabled is equal to a DALY of 0.5. In the year 2000 there were an estimated 9 million osteoporotic fractures world-wide of which 1.6 million were at the hip, 1.7 million at the forearm and 1.4 million were clinical vertebral fractures. The total DALYs lost was 5.8 million accounting for 0.83% of the global burden of non-communicable disease. In Europe osteoporotic fractures account for 2 million DALYs annually, somewhat more than accounted for by hypertensive heart disease and rheumatoid arthritis [19], but less than chronic obstructive pulmonary diseases (Fig. 5). With the exception of lung cancer, fractures due to osteoporosis account for more combined deaths and morbidity than any cancer type (Fig. 6). Collectively, osteoporotic fractures account for approximately 1% of the DALYs attributable to non-communicable diseases in Europe.

Fig. 5 Burden of diseases estimated as disability-adjusted life years (DALYs) in 2002 in Europe [19]



IHD: Ischemic heart disease, COPD: Chronic obstructive pulmonary disease, OA: Osteoarthritis, HD: heart disease, RA: Rheumatoid arthritis, BPH: Benign prostatic hyperplasia

Fig. 6 Burden of diseases estimated as disability-adjusted life years (DALYs) for osteoporosis and specific sites of cancer in 2002 in Europe [19]



1.4.1 The future burden

The frequency of osteoporotic fracture is rising in many countries. Reasons for this relate in part to the increased longevity of the population, which is occurring both in the developed and underdeveloped world. In Europe, the total population will not increase markedly over the next 25 years, but the proportion accounted for by the elderly will increase by 33%. In the developing world, the total population as well as life expectancy of the elderly will increase by more than two-fold over the next 25 years, so that osteoporotic fractures will assume even greater significance for health care planning.

Over and above the increasing population at risk, there is an increase in age- and sex-specific incidence in many communities [44]. Thus, the number of hip fractures has been estimated to more than double assuming no change in age-specific risk [45] but would more than quadruple with very conservative estimates of the secular trend [44, 45] (Table 4).

Table 4 Number of hip fractures estimated world-wide for the year 2000 and those projected by demographic changes alone and those assuming additional increases in age- and sex-specific risk [45]

Year	Scenario	Hip fractures (thousands)	Increment
2000	Base case	1,503	1
2050	Age effect	4,493	3
	1% secular trend	8,162	5.4
	2% (0% Europe & US)	12,335	8.2
	3% (0% Europe & US)	21,310	14.2

As is the case for the variations in fracture risk between populations, the reasons for changes in age- and sex-specific risks over time are unknown. Rates have risen in the Western world but over the past decade or so have levelled off and, in some cases, decreased with calendar year. By contrast, rates appear to be increasing in other regions of the world [46]. Thus improvements in socio-economic prosperity that in turn decrease everyday levels of physical activity may be the cause of increasing fracture rates [47].

1.5 Imperfect health care practice

The ultimate goal of osteoporosis management is to reduce the future risk of fracture. Against this background, there have been a number of advances, particularly in the diagnosis of osteoporosis, the assessment of fracture risk, the development of interventions that reduce the risk of fractures and the production of practice guidelines (reviewed in Chapter 2). Notwithstanding, a minority of patients at high fracture risk are identified for treatment [48–51]. For example, a Canadian study of emergency department radiographs found that only 55% of vertebral fractures were mentioned in the radiology report [52]. In patients with a fragility fracture, less than 20% of individuals receive therapies to reduce future fracture within the year following fracture [49, 53–56]. Paradoxically, the therapeutic care gap is wider in the elderly in whom the importance and impact of treatment is high; studies have shown that as few as 10% of such women with

fragility fractures receive any osteoporosis therapy (estrogens not considered) [48, 57, 58]. Furthermore, treatment rates following a fracture are lower for those individuals who reside in long term care [49]. This contrasts with myocardial infarction, which overcame a significant care gap over the past 15 years; 75% of individuals now receive beta blockers to help prevent recurrent myocardial infarction [59].

The poor access to treatments is compounded by poor adherence to treatment [60, 61]. Approximately 50% of patients do not follow their prescribed treatment regimen and/or discontinue treatment within 1 year [60]. As would be expected, poor adherence is associated with reduced anti-fracture efficacy [62]. The determinants of low persistence and compliance to treatment are not well understood. Dosing requirements and frequency, adverse events, the patient-physician relationship, and patient inability to detect improvements in an asymptomatic disease are factors, but constitute a minority of the variance [25, 63–67]. Retrospective studies indicate that weekly dosing regimens are associated with somewhat greater persistence than daily regimens [68]. It is not yet known whether recently developed treatments given quarterly (i.v. ibandronate), 6-monthly (denosumab), or annual (zoledronic acid) are associated with further improvements in persistence over the long term. Patient education is also important in this respect and nurse-led monitoring early in the course of treatment has been shown to improve compliance [69]. Whether monitoring by measurement of biochemical markers of bone turnover provides additional benefits has not been established [70–72].

1.6 Aims of the report

Osteoporosis represents a major non-communicable disease of today that is associated with economic prosperity, and is set to increase markedly in the future. There is under-utilisation of the measures available to combat the disease and there is therefore a need for assessment of best practices in prevention and treatment, and the adoption of these across countries can potentially result in significant reductions in the burden of this disease. This report reviews country-specific information on the application of new technologies in osteoporosis, the epidemiology of fracture, future trends, and the uptake of treatments. The aim is to quantify the burden of osteoporosis in terms of prevalence, fractures, patients at risk, uptake of treatment, mortality and the societal costs in different countries using a common methodology. The countries reviewed comprise the larger populations of Europe (Spain, Italy, France, Germany and the UK) and Sweden wherefrom many epidemiological and health economic data are available. It is expected that subsequent reviews will extend this outreach.

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2 Medical innovation and clinical progress in the management of osteoporosis

Summary

In recent years, there has been a number of advances, particularly in the measurement of BMD, diagnosis of osteoporosis, the assessment of fracture risk, the development of interventions that reduce the risk of fractures and the production of practice guidelines. This chapter describes the current state of these aspects in the field of osteoporosis. Also, the cost-effectiveness of osteoporosis treatments is addressed.

The key messages of this chapter are:

Ideally, clinical assessment of the skeleton should capture different aspects of fracture risk but at present the assessment of bone mass is the only aspect that can be readily measured in clinical practice.

BMD is the amount of bone mineral per unit volume (volumetric density, g/cm^3), or per unit area (areal density, g/cm^2), and both can be measured in vivo by densitometric techniques.

There are significant differences in the performance of different techniques at different skeletal sites. In addition, the performance depends on the type of fracture that is to be predicted. For example, BMD assessments by DXA to predict hip fracture is better when measurements are made at the hip rather than at the spine or forearm.

In 1994 and 2008, the WHO published diagnostic criteria for osteoporosis in postmenopausal women based on the T-score, intended primarily for descriptive epidemiology.

Based on these diagnostic criteria, osteoporosis is present in approximately 20% of all postmenopausal Caucasian women and 50% of those aged 80 years.

An audit of DXA resources in the 27 member states of the European Union revealed that about 60% had the recommended number of DXA machines for their population.

The use of bone mass measurements for prognosis depends upon accuracy. Accuracy in this context is the ability of the measurement to predict fracture. The ability of BMD to predict fracture is comparable to the use of blood pressure to predict stroke, and significantly better than serum cholesterol to predict myocardial infarction.

Algorithms that integrate the weight of clinical risk factors (CRFs) for fracture risk, with or without information on BMD, have been developed. The FRAX® tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture.

Major pharmacological interventions are bisphosphonates, strontium ranelate, raloxifene, denosumab and parathyroid hormone peptides

Fracture prevention with generically priced alendronate in women aged 50 years and older at high risk of fracture is cost-effective in most Western countries. Other treatments are cost-effective alternatives to no

treatment, particularly in patients that cannot use this treatment.

Compliance and persistence with treatment for osteoporosis are poor; approximately 50% of patients do not follow their prescribed treatment regimen and/or discontinue treatment within one year.

Treatments that could improve adherence will lead to more avoided fractures and are cost-effective complements to currently available treatments.

In all national treatment guidelines some case-finding approach is suggested for patient identification. However, they vary in terms of which risk factors are acknowledged, how the fracture risk should be assessed and how BMD measurements should be used.

Notwithstanding the availability of guidelines, recommendations in national guidelines are not always implemented.

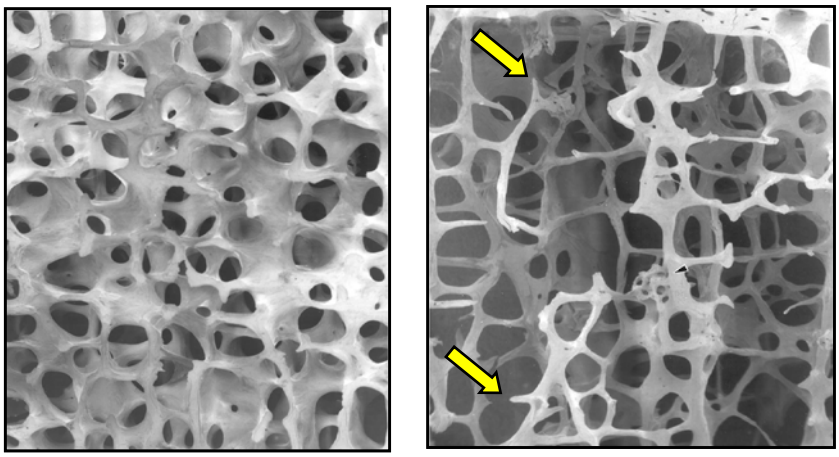
2.1 Introduction

In recent years, there has been a number of advances, particularly in the measurement of BMD, the diagnosis of osteoporosis, the assessment of fracture risk, the development of interventions that reduce the risk of fractures and the production of practice guidelines.

2.2 Measurement of BMD

The description of osteoporosis captures the notion that low bone mass is an important component of the risk of fracture, but that other abnormalities occur in the skeleton that contribute to skeletal fragility (Fig. 7). Ideally, clinical assessment of the skeleton should capture all these aspects of fracture risk but at present the assessment of bone mass is the only aspect that can be readily measured in clinical practice, and forms the cornerstone for the general management of osteoporosis being used for diagnosis, risk prediction, the selection of patients for treatment and monitoring of patients on treatment [1].

Fig. 7 Light microscopic views of normal (left) and osteoporotic (right) cancellous bone. Osteoporosis is associated with thinning of trabecular elements. The resulting destruction of interconnecting elements (arrows) weakens the strength of bone out of proportion to the amount of bone lost (Courtesy of Professor DW Dempster, New York).



BMD is the amount of bone mass per unit volume (volumetric density, g/cm^3), or per unit area (areal density, g/cm^2), and both can be measured *in vivo* by densitometric techniques. A large variety of techniques is available but the most widely used techniques by far are based on x-ray absorptiometry in bone, particularly dual-energy x-ray absorptiometry (DXA). DXA is based on the fact that the absorption of x-rays is very sensitive to the calcium content of tissue, of which bone is the most important source. Other techniques include quantitative ultrasound (QUS), quantitative computed tomography (QCT) applied both to the spine and hip and to the appendicular skeleton (pQCT), peripheral DXA, digital x-ray radiogrammetry and radiographic absorptiometry [2]. DXA is versatile in the sense that it can be used to assess bone mineral content of the whole skeleton as well as specific sites, including those most vulnerable to fracture [3]. DXA provides a two-dimensional areal value rather than a volumetric density and thus is influenced by bone size as

well as true density. The most commonly measured sites are the lumbar spine (L1-L4) and the proximal femur. However, in older people the accuracy of measurements in the lumbar spine may be impaired by scoliosis, vertebral deformity, osteophytes and extraskeletal calcification and the proximal femur is the preferred site.

The widespread clinical use of DXA, particularly at the proximal femur and lumbar spine, arises from many prospective studies that have documented a strong gradient of risk for fracture prediction. For example, a widely cited meta-analysis [4] indicated that the risk of hip fracture increased 2.6-fold for each standard deviation (SD) decrease in BMD. This gradient of risk is better than many other techniques, and the use of central DXA predicts other types of fracture with as high a gradient of risk as other competing techniques.

DXA measurements at the hip have particular utility in the diagnosis of osteoporosis (described later), but measurements at the lumbar spine are also widely used. In early postmenopausal women in whom vertebral fractures are common, vertebral fractures may be predicted with greater effect by measurements at the lumbar spine than with measurements made at the hip. Also, spinal measurements are sensitive to treatment-induced changes, and the spine represents the most widely used site for monitoring the response to treatment. DXA techniques on the lateral spine rather than in the customary postero-anterior projection are increasingly used to detect vertebral fractures [5, 6].

2.2.1 Performance characteristics of bone mineral measurements

The performance characteristics of many measurement techniques have been well documented [2, 4, 7, 8]. For the purpose of risk assessment and for diagnosis, the characteristic of major importance is the ability of a technique to predict fractures. This is traditionally expressed as the increase in relative risk per SD unit decrease in BMD measurements. This is termed the gradient of risk.

There are significant differences in the performance of different techniques at different skeletal sites. In addition, the performance depends on the type of fracture that is to be predicted [4]. For example, BMD assessments by DXA to predict hip fracture are better when measurements are made at the hip rather than at the spine or forearm (Table 5). For the prediction of hip fracture, the gradient of risk provided by hip BMD is 2.6. In other words, the fracture risk increases 2.6-fold for each SD decrease in hip BMD. Thus, an individual with a Z-score of −3 at the hip would have a 2.6^3 or greater than 15-fold higher risk than an individual of the same age with a Z-score of 0 (i.e., an average BMD). Where the intention is to predict any osteoporotic fracture, the commonly used techniques are comparable: the risk of fracture increases approximately 1.5-fold (95% CI = 1.4-1.6) for each SD decrement in the measurement. Thus, an individual with a measurement of 3 SD below the average value for age would have a 1.5^3 or greater than 3-fold higher risk than an individual with an average BMD. Note that the risk of fracture in individuals with an average BMD is lower than the average fracture risk, since BMD is normally distributed whereas the risk of fracture increases exponentially with decreasing BMD.

Table 5 Age-adjusted increase in risk of fracture (with 95% CI) in women for every 1 SD decrease in BMD (by absorptiometry) below the mean value for age [4]

Site of measurement	Outcome fracture			
	Forearm	Hip	Spine	All fractures
Distal radius	1.7 (1.4–2.0)	1.8 (1.4–2.2)	1.7 (1.4–2.1)	1.4 (1.3–1.6)
Femoral neck	1.4 (1.4–1.6)	2.6 (2.0–3.5)	1.8 (1.1–2.7)	1.6 (1.4–1.8)
Lumbar spine	1.5 (1.3–1.8)	1.6 (1.2–2.2)	2.3 (1.9–2.8)	1.5 (1.4–1.7)

2.2.2 Diagnosis of osteoporosis

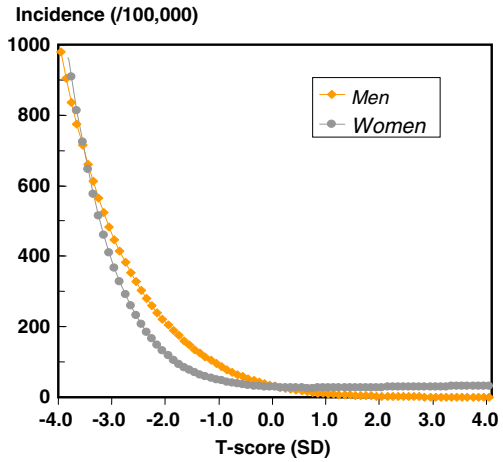
Total skeletal mass and density remain relatively constant once growth has ceased, until the age of 50 years or so. The distribution of bone mineral content or density in young healthy adults ("peak bone mass") is approximately normally distributed, irrespective of the measurement technique used. Because of this normal distribution, bone density values in individuals may be expressed in relation to a reference population in SD units. When SDs are calculated in relation to the mean of a young healthy population, this is referred to as the T-score. In 1994, the WHO published diagnostic criteria for osteoporosis in postmenopausal women based on the T-score, intended primarily for descriptive epidemiology (Table 6) [2, 9]. These criteria have since been widely accepted and are commonly used, perhaps incorrectly, to provide intervention thresholds.

Table 6 WHO's diagnostic thresholds for BMD at the spine, hip or distal forearm

Diagnosis	BMD T-score (SD units)
Normal	≥ −1
Low bone mass (osteopenia)	< −1 but >−2.5
Osteoporosis	≤ −2.5
Severe osteoporosis	≤ −2.5 plus one or more fragility fractures

These thresholds were developed for measurements of BMD at the spine, hip, or forearm. They are inappropriate for use in children or adolescents. More recently, the working definition of osteoporosis has been refined with the femoral neck being proposed as the standard measurement site and the reference population for both men and women being the mean and SD values in young women from the NHANES III study [10, 11]. Reasons for adopting the femoral neck as a reference site include the high predictive value for hip fracture risk (see Table 5) and the wide experience with this site [1]. Measurements at any site (hip, spine and wrist) predict any osteoporotic fracture equally well with a gradient of risk of approximately 1.5 per SD decrease in BMD. The use of a single reference range to compute T-scores in both men and women is merited by the fact that age-specific fracture risk of hip fracture and other osteoporotic fractures is similar in men and women with the same femoral neck BMD (Fig. 2) [12]. However, women do have lower BMD on average and consequently higher fracture risk.

Fig. 8 The age-adjusted incidence of hip fracture according to femoral neck BMD in men and women from 9 population based cohorts in different regions of the world (derived from [12])



Based on these diagnostic criteria, osteoporosis is present in approximately 20% of all postmenopausal Caucasian women and 50% of those aged 80 years. The prevalence of osteoporosis in Sweden using the WHO criteria is shown for Swedish men and women in Table 7 [13]. Approximately 6% of men and 21% of women aged 50–84 years are classified as having osteoporosis. The prevalence of osteoporosis in men over the age of 50 years is 3-times less frequent than in women – comparable to the difference in lifetime risk of an osteoporotic fracture in men and women.

Table 7 Prevalence of osteoporosis at the age intervals shown in Sweden using female-derived reference ranges at the femoral neck [13]

	Men		Women	
Age range (years)	% of population	Number affected (thousands)	% of population	Number affected (thousands)
50-54	2.5	7	6.3	17
55-59	3.5	7.6	9.6	21.1
60-64	5.8	11.4	14.3	30
65-69	7.4	14.2	20.2	43.7
70-74	7.8	14.6	27.9	63
75-79	10.3	13.7	37.5	68.3
80-84	16.6	14.7	47.2	67.8
50-80	6.3	83.2	21.2	310.9

In addition to categorising individuals as having osteoporosis or not, a much more important use of bone mineral measurement is to provide prognostic information of future fracture risk (section 1.2). A further use is as a monitoring tool by which to monitor changes in bone mass in a treated or untreated patient, though this remains a somewhat contentious issue [14–16].

2.2.3 Availability of DXA

The requirement for assessing and monitoring the treatment of osteoporosis to service practice guidelines has been estimated at 10.6 DXA units per million of the general population [17, 18]. The figures assume a case finding approach rather than population based screening. This requirement can be compared with the availability of DXA in different European countries as reported by members of the EU osteoporosis consultation panel in 2008 [19]. The audit revealed that about 60% had the recommended number of DXA machines for their population (Fig. 9). Reimbursement for DXA scans varied widely between member states both in terms of the criteria for and level of reimbursement but only a minority of countries (9/27) provided full reimbursement under any circumstances. It is important to note that the figures provided do not distinguish machines dedicated in part or in full to clinical research, or machines that lie idle or are underutilised because of lack of funding. It is likely, therefore, that the majority of countries are under-resourced in the context of practice guidelines. A further consideration is the inequity of geographical location, which is known to be problematic in Italy, Spain and the UK. This inequity results in long waiting times or long distances to travel or, in many cases, no practical access at all. The density of DXA equipment estimated for 2010 in EU5 and Sweden is shown in Table 8 [20].

Fig. 9 Density (units/million of the population) of central DXA (spine/hip) units in EU as reported in 2007 [19]

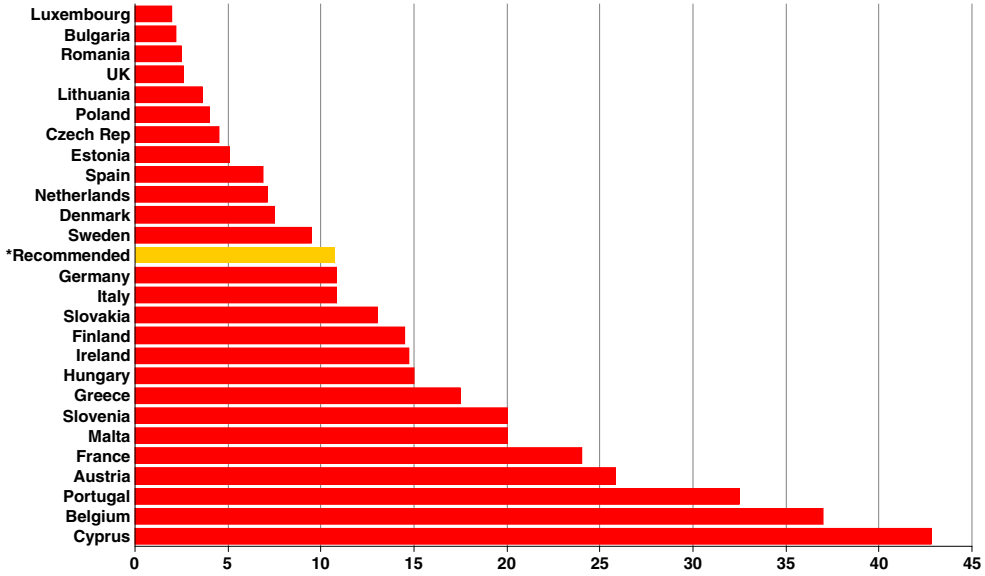


Table 8 Density (units/million of the population) of DXA units in EU5 and Sweden estimated for 2010 [20]

	DXA units	Population (000) [a]	Units/million population
France	1,823	62,637	29.1
Spain	382	45,317	8.4
UK	508	61,899	8.2
Sweden	93	9,293	10
Germany	1,732	82,057	21.1
Italy	1,116	60,098	18.6

[a] Population for 2010 (UN 2008)

2.3 Assessment of fracture risk

Although the diagnosis of the disease relies on the quantitative assessment of BMD which is a major determinant of bone strength, the clinical significance of osteoporosis lies in the fractures that arise. In this respect, there are some analogies with other multifactorial chronic diseases. For example, hypertension is diagnosed on the basis of blood pressure whereas an important clinical consequence of hypertension is stroke. Because a variety of non-skeletal factors contributes to fracture risk [2, 21], the diagnosis of osteoporosis by the use of BMD measurements is at the same time an assessment of a risk factor for the clinical outcome of fracture. For these reasons there is a distinction to be made between the use of BMD for diagnosis and for risk assessment.

2.3.1 Assessing risk with BMD

The use of bone mass measurements for prognosis depends upon accuracy. Accuracy in this context is the ability of the measurement to predict fracture. As reviewed above, many prospective population studies indicate that the risk for fracture increases by a factor of 1.5 to 3.0 for each SD decrease in BMD (see Table 5). The ability of BMD to predict fracture is comparable to the use of blood pressure to predict stroke, and significantly better than serum cholesterol to predict myocardial infarction [4]. The highest gradient of risk is found at the hip to predict hip fracture where the gradient of risk is 2.6.

Despite these performance characteristics, it should be recognised that, just because BMD is normal, there is no guarantee that a fracture will not occur – only that the risk is lower. Conversely, if BMD is in the osteoporotic range, then fractures are more likely, but not invariable. The principal difficulty is that BMD alone has high specificity but low sensitivity, so that the majority of osteoporotic fractures will occur in individuals with BMD values above the osteoporosis threshold [22–25]. At the age of 50 years, the proportion of women with osteoporosis who will fracture their hip, spine or forearm or proximal humerus in the next 10 years (i.e., positive predictive value) is approximately 45%. The detection rate for these fractures (sensitivity) is, however, low and 96% of such fractures would occur in women without osteoporosis [26] (Table 9). The low sensitivity is one of the reasons why widespread population-based screening is not recommended in women at the time of the menopause.

Table 9 Estimates of positive predictive value (PPV), sensitivity, and specificity of measurements to predict any osteoporotic fracture over 10 years or to death in women aged 50 years or 65 years, according to different population cut-offs to define a high-risk category [26]

	High-risk category (% of population)								
	5			10			15		
Gradient of risk (RR/SD)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)
Women aged 50 years									
1.5	12.7	10.7	95.4	10.7	18	90.5	10.3	26.1	85.7
2	19.2	16.2	95.7	15.1	25.5	91	13.8	35.1	86.3
2.5	24.8	21	96	18.7	31.6	91.4	16.5	41.9	86.7
3	29.4	24.9	96.3	21.5	36.3	91.7	18.5	47	87
4	35.8	30.3	96.6	25.1	42.3	92	20.9	52.9	87.4
5	39.5	33.4	96.8	26.8	45.3	92.2	21.8	55.2	87.5
6	41.5	35	96.9	27.5	46.5	92.3	21.9	55.6	87.6
Women aged 65 years									
1.5	28.8	10.2	95.9	24.4	17.3	91.2	23.7	25.3	86.7
2	40.8	14.5	96.6	32.9	23.4	92.2	30.7	32.7	87.9
2.5	49.8	17.7	97.1	39	27.7	92.9	35.4	37.7	88.7
3	56.2	19.9	97.4	43.1	30.6	93.4	38.3	40.8	89.2
4	63.5	22.6	97.9	47.5	33.8	93.9	41.2	43.8	89.7
5	67	23.8	98.1	49.2	34.9	94.1	41.7	44.4	89.8
6	68.5	24.3	98.2	49.4	35.1	94.1	41.2	43.8	89.7

2.3.2 Age and the risk of fracture

The performance characteristics of the test can, however, be improved by the concurrent consideration of risk factors that operate independently of BMD. Perhaps the best example is age. The vast majority of hip fractures (90%), for example, occur in people aged 50 years and older [27]. While this partly relates to the age-related decrease in BMD, age is also a risk factor that is independent of bone mineral density. In other words, at any given BMD, an older adult is much more likely to suffer a fracture than younger people. For example, poor balance and weaker muscles in the elderly contribute to the risk of falls and subsequent fractures. The same T-score with the same technique at any one site has, therefore, a different significance at different ages [26, 28], indicating that age contributes to risk independently of BMD. In addition, the performance characteristics of BMD vary with age. For example, at the age of 50 years, hip fracture risk increased 3.7-fold per SD decrease in femoral neck BMD whereas at the age of 80 years the gradient of risk is 2.3 [12]. The impact of age on hip fracture probability is shown in Table 10. Thus, the consideration of age and BMD together increases the range of risk that can be identified.

Table 10 Ten-year probability of hip fracture (%) in men and women from Sweden according to age and T-score for BMD at the femoral neck (Johnell et al. 2005 [12] and 2007 Table from the erratum)

	T-score (SD units)					
Age (years)	1	0	-1	-2	-3	-4
Men						
50	0.1	0.2	0.8	2.6	8.6	26.6
60	0.1	0.4	0.9	2.5	6.7	17.1
70	0.5	1.2	2.5	5.4	11.4	23
80	1.8	3.2	5.7	10	17.2	28.5
Women						
50	0	0.1	0.3	0.9	3.2	10.7
60	0.1	0.3	0.8	2.3	6.7	18.9
70	0.3	0.8	2.1	5.2	12.8	29.4
80	1.1	2.3	4.8	9.9	19.8	36.9

There are, however, a large number of additional risk factors that provide information on fracture risk independently of both age and BMD.

2.3.3 Other clinical risk factors

A large number of additional risk factors for fracture have been identified. In general, risk factor scores show relatively

poor specificity and sensitivity in predicting either bone mineral density or fracture risk [29, 30]. For the purposes of risk assessment, interest lies in those factors that contribute significantly to fracture risk over and above that provided by bone mineral density measurements or age [31]. A caveat is that some risk factors may not identify a risk that is amenable to particular treatments, so that the relationship between absolute probability of fracture and reversibility of risk is important [32]. Liability to falls is an appropriate example where the risk of fracture is high, but treatment with agents affecting bone metabolism may have little effect.

Over the past few years a series of meta-analyses has been undertaken to identify CRFs that could be used in case finding strategies with or without the use of BMD. These are summarised in Table 11 with their predictive value for hip fracture risk [33].

Table 11 Risk ratio (RR) for osteoporotic fracture and 95% confidence intervals associated with risk factors adjusted for age, with and without adjustment for BMD [33]

Risk indicator	Without BMD		With BMD	
	RR	95% CI	RR	95% CI
Body mass index (20 v 25 kg/m^2)	1.27	1.16-1.38	1.02	0.92-1.13
(30 v 25 kg/m^2)	0.89	0.81-0.98	0.96	0.86-1.08
Prior fracture after 50 years	1.86	1.72-2.01	1.76	1.60-1.93
Parental history of hip fracture	1.54	1.25-1.88	1.54	1.25-1.88
Current smoking	1.29	1.17-1.43	1.13	1.00-1.25
Ever use of systemic corticosteroids	1.65	1.42-1.90	1.66	1.42-1.92
Alcohol intake 3 or more units daily	1.38	1.16-1.65	1.36	1.13-1.63
Rheumatoid arthritis	1.56	1.20-2.02	1.47	1.12-1.92

(a) A low body mass index (BMI) is a significant risk factor for hip and other fractures. For hip fracture, the risk is nearly 2-fold increased comparing individuals with a BMI of 25 kg/m^2 and 20 kg/m^2 [34] (Table 11). It is important to note that comparison of 25 versus 30 kg/m^2 is not associated with a halving of risk, i.e., leanness is a risk factor rather than obesity being a protective factor. Higher BMI is, in fact, protective for bone status, but the effect is very small and a BMI over 30 kg/m^2 is associated with cardiovascular disease and diabetes. The value of BMI in predicting fractures is very much diminished when adjusted for BMD.

(b) One of the best predictors that the skeleton will fail in the future is previous failure i.e., a prior fracture. This is true for both men and women. In the presence of a prior fracture, individuals are almost twice as likely to have a second or further fracture compared to those who are fracture free [35, 36] (Table 12). The increase in risk is even more marked for a vertebral fracture following a previous symptomatic spine fracture. It is important to be aware that up to half of all vertebral fractures are asymptomatic but still impact significantly on future fracture risk [5, 37, 38]. The increase in fracture risk appears to be highest immediately after a fracture event, particularly in the first year [39–41]. The risk decreases over subsequent years, but remains higher than that of the general population. The risks are in part independent of BMD. In general, adjustment for BMD decreases the relative risk by 10% to 20%.

Table 12 Risk of fracture at the sites shown according to the site of a prior fracture (adapted from Klotzbeucher et al [35])

	Site of subsequent fracture									
	Distal forearm		Spine		Proximal humerus[c]		Hip		Pooled	
Site of prior fracture	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Forearm	3	2.0-5.3	1.7	1.4-2.1	2.4	1.7-3.4	1.9	1.6-2.2	2	1.7-2.4
Spine	1.4	1.2-1.7	4.4	3.6-5.4	1.8	1.7-1.9	2.3	2.0-2.8	1.9	1.7-2.3
Humerus[c]	1.8	1.3-2.4	1.9	1.3-2.8	1.9	1.3-2.7	2	1.7-2.3	1.9	1.7-2.2
Hip	1.4	[a]	2.5	1.8-3.5	1.9	[b]	2.3	1.5-3.7	2.4	1.9-3.2
Pooled	1.9	1.3-2.8	2.0	1.6-2.4	1.9	1.6-2.2	2.0	1.9-2.2	2.0	1.8-2.1

[a]No studies;
[b]One study
[c]Assumed to be equivalent to a 'minor fracture' from the meta-analysis

(c) Genetics appear to play a large part in the determination of bone mass and fracture risk. A family history of fragility fractures is a significant risk factor that is largely independent of BMD [42]. A family history of hip fracture is a stronger risk factor than a family history of other osteoporotic fractures and is independent of BMD. It is not known whether genetic factors govern the marked variation in fracture risk seen in different regions of the world. The disease is more common in Caucasian and Asian populations, and the incidence of hip and spine fracture is lower in Africans than Caucasians [43].

(d) Smoking is a risk factor that is in part dependent on BMD. Smoking increases the risk for hip fracture by up to 1.5-fold [44]. As with alcohol, some of the risk associated with smoking is due to decreased BMD and this is particularly true in postmenopausal women where smokers show a much more rapid decline in BMD than non-smokers [45]. Some of the risk associated with smoking is also due to leanness or low BMI.

(e) Glucocorticoids are an important cause of osteoporosis and fractures [46]. The fracture risk conferred by the use of glucocorticoids is, however, not solely dependent upon bone loss and BMD independent risks have been identified.

(f) The relationship between alcohol intake and fracture risk is dose-dependent [47]. Where alcohol intake is on average two units or less daily there is no increase in risk. Indeed, some studies suggest that BMD is higher and, by implication, that fracture risk may be reduced. Intakes of 3 or more units daily are associated with a dose-dependent increase in risk.

(g) There are many secondary causes of osteoporosis (e.g. inflammatory bowel disease, endocrine disorders), but in most instances it is uncertain to what extent the increase in fracture risk is dependent on low BMD or other risk factors such as the use of glucocorticoids. By contrast, rheumatoid arthritis causes a fracture risk independently of BMD and the use of glucocorticoids [48].

(h) Most fractures occur after a fall. Whereas some studies report that falls may be prevented by multi-dimensional interventions, the evidence that these reduce the risk of fracture is plausible but not proven in meta-analysis [49, 50], with the possible exception of exercise interventions. There is also evidence that vitamin D may decrease the risk of fracture by preventing falls [51], but this is uncertain [49]. Other studies have suggested hip fracture risk was not significantly decreased in patients over the age of 80 years given a bisphosphonate, the majority of whom were purportedly selected on the basis of falls risk [52].

2.3.4 Biochemical assessment of fracture risk

Bone markers are increased after the menopause, and in several studies the rate of bone loss and fracture risk varies according to the marker value [53]. Thus, a potential clinical application of biochemical indices of skeletal metabolism is in assessing fracture risk [54]. Some prospective studies have shown an association of osteoporotic fracture with indices of bone turnover independent of bone mineral density in women at the time of the menopause and elderly women [8]. At present, however, the biovariability and measurement variance of bone turnover markers preclude their use in clinical practice as a tool for fracture prediction in individual patients [55].

2.4 Integrating risk factors

Independent risk factors used with BMD can enhance the predictive information provided by BMD alone [56]. Conversely, some strong BMD-dependent risk factors can, in principle, be used for fracture risk assessment in the absence of BMD tests. Thus the consideration of well-validated risk factors, with or without BMD, is a very useful step in improving the targeting of treatment and prevention strategies to those at highest risk. Similar approaches are widely used in other disease areas including cardiovascular disease (e.g., the Framingham calculator) [57] and in the management of primary breast cancer (e.g., Adjuvant! Online, Nottingham Prognostic Index etc.).

The multiplicity of these risk factors poses challenges in the units of risk to be used. The T-score becomes of little value in that different T-score thresholds for treatment would be required for each combination of risk factors. Although the use of relative risks is feasible, the metric of risk best suited for clinicians is the absolute risk (or probability) of fracture.

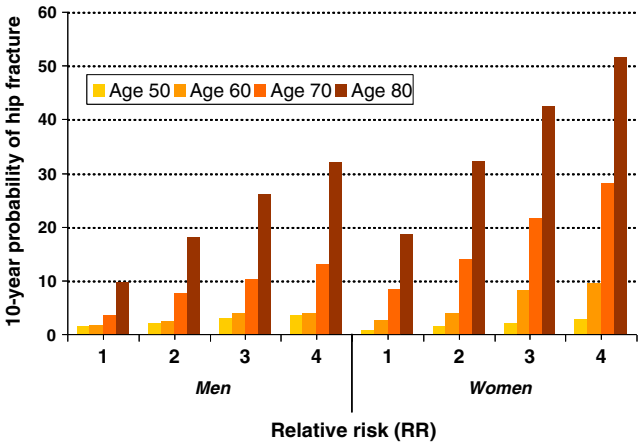
The probability of fracture depends upon age and life expectancy as well as the current relative risk. In general, remaining lifetime risk of fracture decreases with age especially after the age of 70 years, since the risk of death with age outstrips the increasing incidence of fracture with age. Estimates of lifetime probability are of value in considering the burden of osteoporosis in the community, and the effects of intervention strategies. For several reasons they are less relevant for assessing risk of individuals in whom treatment might be envisaged [26]. Thus, the International Osteoporosis Foundation (IOF) and the WHO recommend that risk of fracture should be expressed as a short-term absolute risk, i.e. probability

over a ten year interval [58]. The period of 10-years covers the likely duration of treatment and the benefits that may continue once treatment is stopped.

The major advantage of using fracture probability is that it standardizes the output from the multiple techniques and sites used for assessment. The estimated probability will of course depend upon the performance characteristics (gradient of risk) provided by any technique at any one site. Moreover, it also permits the presence or absence of risk factors other than BMD to be incorporated as a single metric. This is important because, as mentioned, there are many risk factors that give information over and above that provided by BMD and age.

The general relationship between relative risk and 10-year probability of hip fracture is shown in Fig. 10. For example, a woman at the age of 60 years has on average a 10-year probability of hip fracture of 2.4%. In the presence of a prior fragility fracture this risk is increased approximately 2-fold and the probability increases to 4.8%.

Fig. 10 Ten-year probability of hip fracture in men and women from Sweden according to age and the risk (RR) relative to the average population. Probabilities are computed without the inclusion of BMD. (Data from [26])



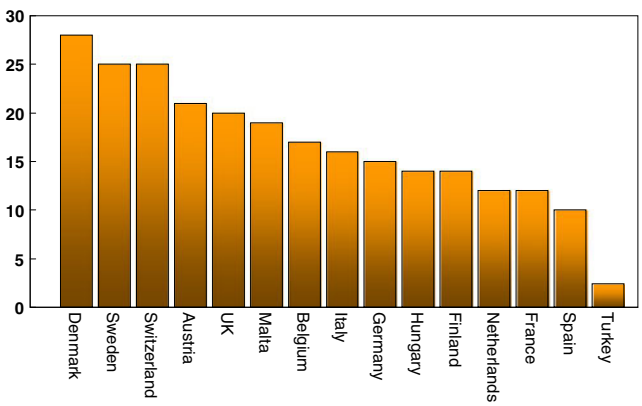
2.4.1 FRAX®

Algorithms that integrate the weight of CRFs for fracture risk, with or without information on BMD, have been developed by the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK [56]. The risk factors used are given in Table 13. The FRAX tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture. A major osteoporotic fracture is a clinical spine, hip, forearm and humerus fracture. Probabilities can be computed for the index countries (including Australia, Austria, Argentina, Belgium, Canada, China, Colombia, Czech Republic, Finland, France, Germany, Hong Kong, Hungary, Italy, Japan, Jordan, South Korea, Lebanon, Malta, Mexico, Netherlands, New Zealand, Philippines, Poland, Romania, Singapore, Spain, Sweden, Switzerland, Taiwan, Tunisia, Turkey, the UK, and US). Where a country is not represented (because of the lack of epidemiological data) a surrogate may be chosen. In Fig. 11 the ten year probability of a major osteoporotic fracture for a 70-year old woman with previous fracture and BMI of 25 kg/m^2 and no other risk factors according to FRAX for various countries is shown as an example.

Table 13 Clinical risk factors used for the assessment of fracture probability [67]

- Age
- Sex
- Low body mass index
- Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
- Parental history of hip fracture
- History of fragility fracture
- Glucocorticoid treatment (≥5 mg prednisolone daily for 3 months or more)
- Current smoking
- Alcohol intake 3 or more units daily
- Rheumatoid arthritis
- Other secondary causes of osteoporosis
  - Untreated hypogonadism in men and women, e.g. premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism
  - Inflammatory bowel disease, e.g., Crohn's disease and ulcerative colitis. It should be noted that the risk is in part dependent on the use of glucocorticoids, but an independent risk remains after adjustment for glucocorticoid exposure.
  - Prolonged immobility, e.g., spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, ankylosing spondylitis
  - Organ transplantation
  - Type I diabetes
  - Thyroid disorders, e.g. untreated hyperthyroidism, over-treated hypothyroidism
  - Chronic obstructive pulmonary disease

Fig. 11 Ten-year probability of a major osteoporotic fracture (%) for a 70-year old woman with previous fracture and BMI of 25 kg/m^2 and no other risk fractures according to FRAX in different European countries



FRAX is also available on densitometers (Hologic, GE Lunar and DSM) and as an application on the i-Phone and i-Pad obtainable through the IOF (http://itunes.apple.com/us/app/frax/id370146412?mt=8). The FRAX pad allows patients to input risk variables prior to medical consultation and is available from the IOF (www.iofbonehealth.org) in several languages. Where computer access is limited, paper charts can be downloaded that give fracture probabilities for each index country (www.shef.ac.uk/FRAX) according to the number of CRFs. Hand held calculators are used in Japan and Poland.

Like any algorithm, FRAX has a number of limitations. These include:

a) *Dose response of risk factors*

Several of the CRFs identified take no account of dose-response, but rather represent an average dose or exposure. For example, there is good evidence that the risk associated with smoking [45], excess alcohol consumption [47], and the use of glucocorticoids [59, 60] increases with increasing exposure, as does the number of prior fractures [35, 38, 61]. Moreover, the risk of a second fracture is much higher immediately after the first event, particularly during the first year after a first fracture [39–41]. Ten-year probabilities will underestimate, therefore, immediate fracture risk after a first fracture, since the risk is integrated over the entire 10-year interval. These limitations should be recognised when interpreting the FRAX result in the clinic [62].

b) *Other measurements of skeletal strength*

At present the FRAX tool limits BMD to that measured at the femoral neck, largely as a result of the wealth of data available for this site. It has the advantage that for any given age and BMD, the fracture risk is approximately the same in men and women. Because of this, the T-score is derived from a single reference standard (the NHANES III database for female Caucasians aged 20–29 years) as widely recommended [58]. There are, however, other bone measurements that provide information on fracture risk, but the available information in the source cohorts was too sparse to provide a meta-analytic framework for the present version of FRAX. Other measurements may be incorporated into risk assessment algorithms when they are more adequately characterised.

c) *Falls and other factors influencing fracture risk*

The current version of FRAX does not incorporate fall-related risk factors, even though falls are known to be a strong risk factor [63–66]. It is therefore important to appreciate that fracture risk may be underestimated to some extent in the presence of a falls history that is higher than average for age. The concern that fracture risk attributed to falls may not be amenable to anti-resorptive therapies such as bisphosphonates [52] is not supported by more recent data [66], but further research is required to clarify this.

Bearing these limitations in mind, FRAX is a well validated tool that can be easily applied in clinical practice and widens the access to the assessment of fracture risk. The application in clinical practice obviously demands a consideration of the fracture probability at which to intervene, both for treatment (an intervention threshold) and for BMD testing (assessment thresholds). Probability-based intervention thresholds have been developed for Europe, but also for individual countries including Canada, Germany, Japan, Sweden, Switzerland, the UK and US [67–73].

The UK guidance for the identification of individuals at high risk of fracture has been developed by the National Osteoporosis Guideline Group (NOGG) (www.shef.ac.uk/NOGG) and its potential application to other EU countries is developed in subsequent chapters.

2.5 Treatment of osteoporosis and prevention of fracture

In recent years there have been significant advances in the management of osteoporosis, particularly with respect to the development of pharmacological interventions to reduce fracture risk.

2.5.1 General management

General management includes the avoidance of modifiable risk factors such as smoking and excessive alcohol intake. Assessment of the risk of falls and their prevention is important in the elderly. An increased likelihood of falls can arise from numerous age- and disease-related factors. Some of these factors, such as

short-sightedness or cataracts, may appear irrelevant but there is good evidence that prompt treatment reduces falls risk [74]. Other disease processes are more difficult to manage including, for example, dementia, strokes and other neurological diseases. Medications, especially sedatives, can impair balance and are significant risk factors for fractures. Environmental factors that can precipitate a fall include slippery or uneven flooring, carpet edges and poor or inadequate footwear. Further, where possible, drugs that induce accelerated bone loss (Table 14) should be avoided or the minimum effective dose titrated.

Table 14 Drugs that increase the risk of osteoporosis

Androgen deprivation therapy
Anticonvulsants
Aromatase inhibitors
Glucocorticoids
High dose thyroxine
Proton pump inhibitors
Selective serotonin reuptake inhibitors
Thiazolidenediones

Immobility is a strong risk factor for osteoporosis [75]. Maintenance of mobility is therefore important. It is not known what constitutes the optimal exercise programme to maintain skeletal mass in health or disease but exercise can also improve posture and balance to protect against both falls and fractures [76].

Correction of nutritional deficiencies, particularly of calcium, vitamin D and protein, are advised. Intakes of at least 1000 mg/day of calcium, 800 IU of vitamin D and of 1 g/kg body weight of protein are widely recommended [58, 77]. The use of calcium, vitamin D and the combination as a therapeutic agent is discussed later.

2.5.2 Major pharmacological interventions

Major pharmacological interventions are bisphosphonates, strontium ranelate, raloxifene, denosumab and parathyroid hormone peptides. Interventions that are approved for the prevention and treatment of osteoporosis in Europe are shown in Table 15. Most of these are approved only for the treatment of postmenopausal osteoporosis. However, alendronate, etidronate, risedronate and zoledronic acid are also approved for the prevention and treatment of glucocorticoid-induced osteoporosis in Europe and alendronate, risedronate, zoledronic acid and teriparatide are approved for the treatment of osteoporosis in men.

Table 15 Pharmacological interventions used in the prevention of osteoporotic fractures

Intervention	Year of market approval	Dosing regimen	Route of administration
Alendronate	1995	70 mg once weekly or 5 or 10 mg once daily	Oral
Etidronate	1980	400 mg daily for 2 weeks every 3 months	Oral
Ibandronate a).	2005	150 mg once monthly	Oral
Ibandronate b).	2005	3 mg once every 3 months	Intravenous injection
Risedronate	2000	35 mg once weekly or 5 mg once daily	Oral
Zoledronic acid	2005	5 mg once yearly	Intravenous infusion
Denosumab	2010	60 mg twice yearly	Subcutaneous injection
Raloxifene	1998	60 mg once daily	Oral
Bazedoxifene	2009	20 mg once daily	Oral
Strontium ranelate	2004	2 gm once daily	Oral
Teriparatide	2003	20 μg once daily	Subcutaneous injection
Parathyroid hormone 1-84	2006	100 μg once daily	Subcutaneous injection

All these interventions have been shown to reduce the risk of vertebral fracture when given with calcium and vitamin D supplements. Some have been shown to also reduce the risk of non-vertebral fractures, or specifically hip fractures. Of the available options, alendronate, risedronate, zoledronic acid, denosumab and strontium ranelate have been demonstrated to reduce vertebral, non-vertebral and hip fractures [52, 78–85] (Table 16). Because of this broader spectrum of anti-fracture efficacy these agents are generally regarded as preferred options in the prevention of fractures in postmenopausal women. This distinction is important because once a fracture occurs, the risk of a subsequent fracture at any site is increased independent of BMD, and hence an intervention that covers all major fracture sites is preferable.

Table 16 Spectrum of anti-fracture efficacy of interventions approved in Europe [67]

	Fracture outcome		
Intervention	Vertebral	Non-vertebral	Hip
Alendronate	+	+	+
Ibandronate	+	+*	NAE
Denosumab	+	+	+
Risedronate	+	+	+
Zoledronic acid	+	+	+
Raloxifene	+	NAE	NAE
Strontium ranelate	+	+	+*
Teriparatide	+	+	NAE
PTH (1–84)	+	NAE	NAE

NAE: not adequately evaluated.

* In subsets of patients (post-hoc analysis)

PTH: recombinant human parathyroid hormone.

Since there have been no head-to-head studies with fracture as the primary outcome, direct comparison of efficacy between agents is not possible. However, the reduction in vertebral fracture rate has generally been between 50 and 70% whereas the magnitude of reduction in non-vertebral fracture, where demonstrated, has generally been smaller and in the order of 15 to 25%. Details of the treatment effects assumed in this report are given in Chapter 6. This difference in effect on different fracture outcomes is likely to reflect, at least in part, the importance of falls in the pathogenesis of these fractures but may also result from differences in the effects of the various treatments on cortical and cancellous bone.

Reduction in fracture risk has been shown to occur within one year of treatment for bisphosphonates, strontium ranelate and denosumab. This is particularly important in the case of vertebral fractures, since after an incident vertebral fracture there is a 20% risk of a further fracture occurring within the next 12 months, emphasizing the importance of prompt treatment once a fracture has occurred [39].

2.5.2.1 Bisphosphonates

Bisphosphonates are synthetic analogues of the naturally occurring compound pyrophosphate and inhibit bone resorption. Alendronate, risedronate, etidronate and ibandronate are available as oral formulations (70 mg once weekly, 35 mg once weekly, 400 mg daily and 150 mg once monthly, respectively). Oral bisphosphonates are generally well tolerated. Upper gastrointestinal side-effects may occur with nitrogen-containing bisphosphonates (alendronate, etidronate, risedronate and ibandronate), particularly if the dosing regimen is not adhered to. It is therefore important that patients take the drug according to the instructions, namely in the morning with a full glass of water, 30–60 minutes before food, drink, or other medications, and remaining standing or sitting upright for that time. Compliance with this dosing regimen is essential to maximise intestinal absorption and prevent the occurrence of upper gastrointestinal side-effects. Oral bisphosphonates are therefore not suitable for very frail patients or those with cognitive dysfunction and are contraindicated in the presence of significant oesophageal disease.

Ibandronate and zoledronic acid are available as intravenous formulations. The former is given as a push injection over 15–30 seconds every 3 months, whereas zoledronic acid is administered as an intravenous infusion over 15 minutes at a dose of 5 mg once yearly. An acute phase reaction may occur, particularly with the first injection, resulting in flu-like symptoms. This is sometimes severe but is self-limiting and can be avoided or reduced in severity by taking paracetamol on the day of the infusion and the subsequent 1–2 days.

Etidronate is generally considered to have the weakest evidence base of the bisphosphonates. It has been shown to reduce vertebral fractures over two years, but not subsequently, with no significant effect on non-vertebral fractures [86].

Anti-fracture efficacy has not been directly shown for the intravenous ibandronate formulation or for the 150 mg once monthly regimen, but is assumed from a bridging study based on BMD changes [87, 88]. Zoledronic acid has been demonstrated to reduce vertebral, non-vertebral and hip fractures in women with postmenopausal osteoporosis and also reduces the incidence of recurrent clinical fractures in patients who have suffered a hip fracture [83, 85].

However, there are potential concerns that long-term suppression of bone turnover associated with treatment may eventually lead to adverse effects on bone strength. This remains largely a theoretical concern although there have been recent reports of atypical stress fractures in the femoral shaft or subtrochanteric region in patients on alendronate therapy; in some of these cases bone biopsies have been done and have shown markedly suppressed bone turnover [89–93]. However, it should be stressed that these fractures are extremely rare and easily outweighed overall by the beneficial effects of alendronate on fracture risk.

A potential side-effect of bisphosphonate therapy that has received much attention is osteonecrosis of the jaw. Whilst it is likely that there is a causal association in patients with malignant disease receiving high doses of intravenous bisphosphonates, this remains unproven in

patients receiving the much lower doses of bisphosphonates used for the treatment of osteoporosis [94]. Since many of the cases reported have been associated with dental disease, invasive dental treatment should be completed before bisphosphonate therapy is started and where possible, avoided during treatment [95–97].

Recently, concerns have been raised about a possible association between bisphosphonate therapy and atrial fibrillation following the report of a significant increase in risk of serious atrial fibrillation in women treated with zoledronic acid in the HORIZON study. Subsequent studies have produced conflicting results but have not excluded the possibility of such an association and further investigation is warranted [98]. Finally, the possibility that bisphosphonate therapy is associated with increased risk of oesophageal cancer has been raised. Two recent studies from the General Practice Research Database in the UK have produced conflicting results, one failing to show any association but another concluding that there was an increased risk with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period [99, 100].

2.5.2.2 Denosumab

Denosumab is a fully humanised monoclonal antibody to receptor activator of NFkB ligand (RANKL). RANKL is a major regulator of osteoclast development and activity. Denosumab prevents the interaction of RANKL with its receptor RANK by binding to RANKL, resulting in rapid and profound inhibition of bone resorption [101]. It has recently been approved in Europe and the US. In the pivotal phase III trial in postmenopausal women with osteoporosis 3 years treatment resulted in fracture reductions of 68%, 20% and 40% for spine, non-vertebral and hip fractures, respectively [78]. The overall incidence of adverse events was similar in the treatment and placebo groups. Eczema, flatulence and cellulitis were more common in the denosumab group compared with placebo (3.0%, 2.2% and 0.3% versus 1.7%, 1.4% and <0.1%, respectively). Osteonecrosis of the jaw has been rarely reported in women treated for osteoporosis with denosumab.

Denosumab is administered as a subcutaneous injection in a dose of 60 mg once every 6 months. This makes it ideal for use in primary care and should encourage greater adherence to treatment than is seen with, for example, oral bisphosphonates.

2.5.2.3 Strontium ranelate

Strontium ranelate is composed of two atoms of stable strontium with ranelic acid as a carrier. Its mechanism of action has not been fully defined. It has been proposed that strontium ranelate both inhibits bone resorption and stimulates bone formation through the activation of the calcium sensing receptor and the OPG/RANKL system [102–104]. The strength of bone may also be due to an improvement of the material or structural properties of bone [105, 106]. Its use is associated with a substantial increase in BMD in the spine and hip, although part of this increase is due to incorporation of strontium into bone, which affects the accuracy of DXA [106].

Strontium ranelate has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women with osteoporosis [80, 81]. In a post hoc analysis in older women with low hip BMD, it was also shown to reduce hip fractures. It is taken as a single daily dose and is generally well tolerated. There is a small increase in the frequency of diarrhoea, nausea and headache. There is also a small increase in the risk of venous thromboembolic disease (RR 1.42 BMD 95% CI 1.02, 1.98) and very rarely, hypersensitivity reactions may occur [107].

2.5.2.4 Raloxifene

Raloxifene is a selective oestrogen receptor modulator that has oestrogenic (anti-resorptive) effects in the skeleton without the unwanted effects of oestrogen in the breast and endometrium. It is taken orally as a single daily dose. Reduction in vertebral, but not non-vertebral or hip fractures, has been demonstrated in postmenopausal women with osteoporosis [108]. Adverse effects include leg oedema, leg cramps, hot flushes and a 2- to 3-fold increase in the risk of venous thromboembolism. Its use is associated with a significant decrease in the risk of breast cancer but a small increase in the risk of stroke [109].

2.5.2.5 Parathyroid hormone peptides

Teriparatide (recombinant human 1–34 parathyroid hormone peptide) and PTH (1–84) (recombinant human 1–84 parathyroid hormone; PTH) are administered by subcutaneous injection in daily doses of 20 μg and 100 μg, respectively. They have anabolic effects on bone, increasing bone formation and producing large increases in BMD in the spine. Teriparatide has been shown to reduce both vertebral and non-vertebral fractures in postmenopausal women with osteoporosis after a median treatment period of 21 months, whereas reduction only in vertebral fractures was shown after 18 months treatment with PTH (1–84) [110, 111]. There are no data demonstrating a reduction in hip fracture. Side-effects include nausea, headache and dizziness; in addition, transient hypercalcaemia and hypercalciuria may occur, particularly with PTH. The treatment period is limited to 24 months. In

general, because of higher cost of these peptides, treatment is restricted to those with severe osteoporosis who cannot tolerate or appear to be unresponsive to other therapies.

2.5.2.6 Hormone replacement therapy (HRT)

Because the risk/benefit balance of HRT is generally unfavourable in older postmenopausal women, it is regarded as a second-line treatment option. However, it is an appropriate option in younger postmenopausal women at high risk of fracture, who also have menopausal symptoms [112].

2.5.2.7 Calcium and vitamin D

Combined calcium and vitamin D supplements in a daily dose of 0.5-1.2 g and 400–800 IU, respectively, are generally recommended in patients receiving bone protective therapy, since most randomised controlled trial evidence for the efficacy of interventions is based on co-administration of the agent with calcium and vitamin D supplements. Effects of calcium and/or vitamin D as monotherapy are considered below.

Calcium
Calcium supplements produce modest increases in BMD and may reduce fractures by a small amount [113]. A recent meta-analysis concluded that calcium supplements without co-administered vitamin D increased the risk of myocardial infarction by around 30% [114]. However, it should be noted that cardiovascular outcomes were not primary end points in any of the studies included in the meta-analysis and data on cardiovascular events were not collected in a systematic manner.

Vitamin D
Vitamin D has been shown to reduce bone loss in older women and in a meta-analysis was found to reduce non-vertebral fractures when given in doses between 400 and 800 IU/day [115]. There is some evidence that fracture reduction is seen only when calcium supplements are co-administered with the vitamin D [116]. A reduction in falls has also been reported in a recent meta-analysis, vitamin D in a dose of 700–1000 IU/day reducing the risk of falling among older individuals by 19% [117]. However, two studies of high doses of vitamin D given annually have demonstrated an increased risk of hip fracture and, in one study, also of falls [118, 119].

2.5.3 Vertebroplasty and balloon kyphoplasty

Vertebroplasty and balloon kyphoplasty are options for the management of acute vertebral fractures [120]. Vertebroplasty consists of the transpedicular placement of bone cement into fractured vertebral bodies, whereas in balloon kyphoplasty a balloon is introduced into the fractured vertebra and inflated to restore vertebral height. Subsequently, the balloon is deflated and the space created is filled with bone cement. Both approaches have been shown to reduce pain and improve functional ability significantly when compared to non-surgical management in patients with acute symptomatic vertebral fractures [121–123]. Balloon kyphoplasty appears to be superior to vertebroplasty with respect to restoration of vertebral height and reduction of spinal deformity, although the clinical and functional significance of the relatively small differences remain to be established.

In the majority of studies, these procedures were compared to non-surgical management. However, in two recent randomized controlled studies, vertebroplasty was compared to a placebo procedure in which the various stages of vertebroplasty were mimicked but without injection of cement. Neither of these studies was able to demonstrate a beneficial effect of vertebroplasty over placebo on pain, functional ability or quality of life [124, 125]. The follow-up period of these studies was relatively short (1 month and 6 months respectively) and it is possible that the long-acting local anaesthetic injected in the placebo group might have provided some pain relief in the placebo group. No placebo-controlled trials have been conducted for balloon kyphoplasty.

In a recent meta-analysis, vertebroplasty was found to have a higher rate of procedure-related complications than balloon kyphoplasty and a higher rate of cement leakage, which may sometimes result in neurological symptoms [124]. A potential concern for both procedures is that the risk of compression fractures in vertebrae adjacent to the operated vertebra might be increased and further long-term studies are required to address this issue. The results of studies so far reported indicate a similar incidence of new vertebral fractures in women who have undergone balloon kyphoplasty or vertebroplasty when compared to non-surgical management but longer term data are required.

2.5.4 Future developments in the treatment and management of osteoporosis

A number of new approaches are being explored for the prevention of fractures in postmenopausal women [126]. These include antibodies to Wnt antagonists including sclerostin [127], cathepsin K inhibitors [128], transdermal PTH peptide formulations [83], and drugs that act on calcium sensing receptors [129]. In addition, there is growing interest in the use of sequential therapy, using anti-resorptive drugs to maintain the benefit of anabolic agents, and using mild anti-resorptives after a period of treatment with potent anti-resorptive drugs such as denosumab.

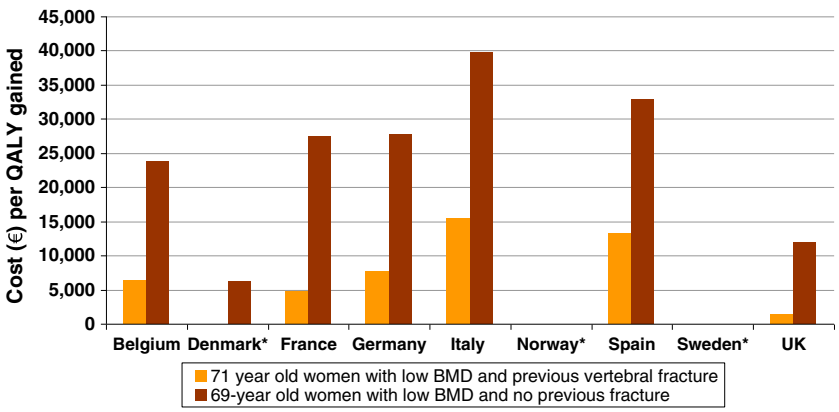
Studies from many parts of the world indicate that osteoporosis is under-recognised and undertreated, with only a minority of patients with fracture receiving appropriate investigation and treatment. Health services research is directed towards addressing the treatment gap by developing more effective models of service delivery. Even though still limited, there has in recent years been an increase in the development of integrated management programs or coordinator-based systems which aim at improving the management of osteoporosis. These programs can consist of several different components such as education, improved screening and testing, more efficient channels to detect patients and follow up after treatment initiation. There are several studies that have shown that these programmes improved osteoporosis management (increased prescription and BMD testing) and reduction in the risk of hip fracture compared to standard management [130–134]. In the few health economic analysis that have been published so far the results have shown that osteoporosis management programmes are a cost-effective intervention for the prevention of fractures [134, 135]. More evidence is needed both on the clinical outcomes and the cost-effectiveness of these programmes; however, it is likely that they will become more widely adopted in the future.

2.5.5 Cost-effectiveness of pharmaceutical interventions

The osteoporosis market is today dominated by bisphosphonates, particularly alendronate, which have become the mainstay first-line choice given its proven efficacy and low price. Bisphosphonates are generally found to be cost-effective in women with osteoporosis, regardless of whether the perspective is societal or not and if the modelling horizon is lifetime or shorter [136].

A pan-European study from 2004 estimated the cost-effectiveness of branded alendronate in nine countries [137]. In this study alendronate was shown to be cost-saving compared with no treatment in women with osteoporosis (with and without previous vertebral fracture) from the Nordic countries (Norway, Sweden, and Denmark). The cost-effectiveness of alendronate compared to no treatment was also within acceptable ranges in Belgium, France, Germany, Italy, Spain and the UK (Fig. 12). However, with the rapid decline in the price of the generic alendronate, analyses based on a branded drug price have become obsolete and would require an update. For example, in the above mentioned study the annual price of alendronate varied between €444/year (UK) to €651/year (Denmark). The current drug price for alendronate is less than €300/year in all countries and even as low as €18/year in the UK (see Chapter 4). Revisiting the analysis using these prices would markedly improve the cost-effectiveness of generic alendronate.

Fig. 12 Cost-effectiveness of branded alendronate compared to no treatment in 2004 [137]



*Cost-saving

In a more recent study from 2008 [138], the cost-effectiveness of alendronate compared with no treatment using a generic price in the UK was assessed by using the FRAX algorithm for fracture risk estimation. Alendronate was in this analysis priced at £95/year and could be considered cost-effective in most age and risk groups (Table 17).

Table 17 Cost-effectiveness of alendronate (cost (£000)/QALY gained) in UK women with CRFs according to age and T-score for femoral neck BMD [138]

	T-score (SD)			
Age	0	-1	-2	-3
Prior fracture				
50	18.1	15.7	9.9	3.2
60	18.4	15.6	10.5	2.6
70	9.0	6.5	3.2	c.s.
80	13.9	7.3	2.3	c.s.
Family history				
50	16.3	14.7	11.1	5.9
60	15.7	14	10.4	5.9
70	9	6	1.8	c.s.
80	5.1	c.s.	c.s.	c.s.
Glucocorticoids				
50	23.3	19.5	13.3	4.6
60	22.3	19.0	12.6	3.1
70	10.6	7.5	2.9	c.s.
80	15.0	6.4	c.s.	c.s.
Rheumatoid arthritis				
50	21.1	22.6	15.4	6.2
60	25.1	21.1	14.4	6.3
70	11.5	8.4	4.4	c.s.
80	15.7	7.8	1.9	c.s.
Alcohol (>3 units/day)				
50	28.5	24.3	16.2	6
60	27.1	22.7	15	6.1
70	12.6	8.9	4.4	c.s.
80	16.1	7.6	1.2	c.s.
Current smoking				
50	37.6	31.7	19.9	6.6
60	37.7	31.1	19.5	6.7
70	18.5	13.1	5.6	c.s.
80	25.8	12.0	0.2	c.s.

c.s. = cost-saving

The cost-effectiveness of a range of treatments has also been evaluated in women with a BMD value meeting or exceeding the threshold of osteoporosis. As seen in Table 18 the cost-effectiveness of alendronate compared with no treatment was better than for the alternatives. This is mainly driven by the drug price rather than because of differences in efficacy between treatments. Thus, the study supports the view that alendronate should be considered as a first line intervention, at least in a UK setting. Nevertheless, cost-effective scenarios were found for treatments other than alendronate, providing credible alternative options for patients unable to take alendronate. Similar conclusions have also been reached in separate studies for most second line treatments [77, 136, 139–146]. There are differences, however, in the spectrum of efficacy of these alternatives across different fracture sites that will determine their suitability in the clinical management of individuals.

Table 18 Cost-per QALY gained (£) of various drugs compared to no treatment in women aged 70 years in the UK [138]

	T-score = −2.5 SD		No BMD
Intervention	No prior fracture	Prior fracture	Prior fracture
Alendronate	3,714	867	2,119
Etidronate	12,869	10,098	9,093
Ibandronate daily	20,956	14,617	14,694
Ibandronate intermittent	31,154	21,587	21,745
Raloxifene	11,184	10,379	10,808
Raloxifene without breast cancer	34,011	23,544	23,755
Risedronate	18,271	12,659	13,853
Strontium ranelate	25,677	18,332	19,221
Strontium ranelate, post-hoc analysis	18,628	13,077	13,673

When considering the body of published evidence, fracture prevention with alendronate in women at elevated risk of fracture older than 50 years is cost-effective in most western countries. Cost-effectiveness improves further in patients with additional risk factors. Fracture risk at a given T-score is similar in men and women [147], the effectiveness of intervention in men is broadly similar to that in women at equivalent risk [148], and the cost and disutility of fractures is similar in men and women [149, 150]. For these reasons the cost-effectiveness of treating men will broadly be the same as for women at a given absolute risk of fracture.

2.5.6 Adherence, compliance and persistence

There is a wide variety of definitions for adherence in the literature. The term compliance is widely used, but it has been argued that the term implies “obedience to doctors” and that it should be termed in a way that also includes the active choice of the patient [151]. In line with this view, a number of alternative terms have been proposed: adherence [152], patient cooperation [153], therapeutic alliance [154] or concordance [155], referring to the agreement between patient and physician. For the purpose of this report the terms compliance and persistence were used to define the following of dosing instructions and the time on treatment, respectively. The term adherence was used as a general term encompassing both of these concepts.

Whilst clinical trials remain the gold standard for measuring fracture reduction, the high internal validity required to demonstrate efficacy comes at the expense of external validity. The results of such trials may therefore generalize poorly to clinical practice [156, 154] since the benefits obtained in practice might fall short of the anticipated benefits indicated by clinical trials. Table 19 summarizes the evidence on persistence for the bisphosphonates from the placebo-controlled studies identified in a systematic review by Lloyd-Jones and Wilkinson [158] of randomised clinical trials (RCTs) which report fracture outcomes in postmenopausal or steroid induced osteoporosis. It is clear, however, that even in randomised trials, persistence with therapy declines over time. Thus, any reduced effectiveness caused by sub-optimal adherence is to some extent already captured in clinical trials.

Table 19 RCTs reporting persistence: percentage of patients in bisphosphonate group still taking bisphosphonate therapy

Study	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Daily alendronate for postmenopausal osteoporosis						
AOPS [159]	89	72	70			
Bone 2000 [160]	NR	74				
EPIC Study [161]	NR	NR	NR	NR	NR	50
Fracture Intervention Trial: women with pre-existing fractures [162]	NR	NR	89			
Fracture Intervention Trial: women without pre-existing fractures [163]	NR	NR	NR	81		
Liberman 1995 [164]	92	89	84			
Lindsay 1999 [165]	95					
Pols 1999 [166]	88					
Rossini 1994 [167]	100					
Cyclical etidronate for postmenopausal osteoporosis						
Herd 1997 [168]	NR	85				
Meunier [169]	NR	89				
Montessori [170]	NR	NR	87			
Pouilles 1997 [171]	NR	83				
Storm [172]	NR	NR	61			
Watts 1990 [173]	NR	83				
Cyclical etidronate for steroid-induced osteoporosis						
Adachi 1997 [174]	82					
Cortet 1999 [175]	98					
Geusens 1998 [176]	NR	72				
Jenkins 1999 [177]	87					
Pitt 1998 [178]	NR	85				
Roux 1998 [179]	88					
Daily risedronate for postmenopausal osteoporosis						
Brown (5 mg dose) [180]	84					
Clemmesen 1997 (2.5 mg dose) [181]	NR	66				
Fogelman 2000 (5 mg dose) [182]	NR	78				
Harris 1999 (5 mg dose) [84]	NR	NR	60			
McClung 2001 (2.5 or 5 mg dose) [55]	NR	NR	51			
Mortensen 1998 (5 mg dose) [183]	86	46				
Reginster 2000 (5 mg dose) [184]	82	NR	62			
Weekly risedronate 35 mg for postmenopausal osteoporosis						
Brown [180]	81					
Daily risedronate for steroid-induced osteoporosis						
Cohen 1999 (5 mg dose) [185]	82					

NR = not reported

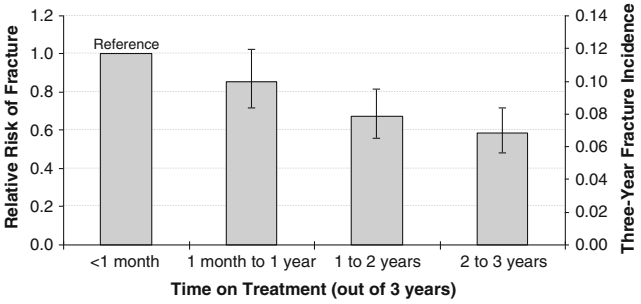
The methods available for measuring adherence are usually broken down into direct and indirect methods of measurement. Each method has advantages and disadvantages, and no method is considered the gold standard [186, 187]. Examples of direct methods of measures of adherence include directly observed therapy, measurement of concentrations of a drug or its metabolite in blood or urine, and detection or measurement in blood of a biological marker added to the drug formulation. Indirect methods of measurement of adherence include asking the patient how easy it was to take the prescribed medication, performing pill counts, ascertaining rates of refilling prescriptions, collecting patient questionnaires, using medication event monitoring systems or asking the patient to keep a medication diary [188].

Because osteoporosis is an asymptomatic disease where only a fraction of the treated patients will sustain a fracture, large samples of patients are needed to detect differences in fracture rates between patients with high and low adherence to medication. Therefore, much of the data presented concerning adherence with anti-fracture medication is based on claims data or data describing filled prescriptions [189–193]. These databases often produce two types of adherence estimates:

1) Persistence, defined as the proportion of patients that at a certain time point still fill prescriptions without a gap in refills longer than an allowed period of time (e.g., 30, 60, or 90 days).
2) Compliance, defined as medication possession ratio (MPR). MPR is usually defined as the number of days of medication available to the patient, divided by the number of days of observation. Estimates of MPR should be interpreted with caution since its meaning differs with the definition of *days of observation*. MPR measures only the frequency and length of refill gaps if the observation time is defined to be the same as a patient's total time on treatment [193]. If *days of observation* is a predefined time period (e.g., 24 months) [190] MPR becomes a composite estimate of persistence and compliance. Although the MPR provides insight into the availability of medication, it does not provide information on the timeliness and consistency of refilling. An MPR > 80% is often used as a threshold for high adherence, where improved clinical outcomes can be observed [190, 194, 195]. However, this threshold originates from a blood pressure control study [196] and has been criticised for being arbitrary when extrapolated to other diseases [197].

Compliance and persistence with treatment for osteoporosis in clinical practice are poor; approximately 50% of patients do not follow their prescribed treatment regimen and/or discontinue treatment within one year [198]. Poor adherence has been shown to be associated with reduced anti-fracture efficacy when expressed both as MPR [190] and as persistence [193, 199]. Fig. 13 shows an analysis from the Swedish Adherence Register Analysis (SARA) study depicting the relation between time on treatment and fracture risk in 37,394 bisphosphonate-treated patients observed for 36 months [193]. The quantum of effect may be overestimated since patients who fail to comply with placebo have poorer health outcomes than compliant patients [200, 201]. In the context of osteoporosis, fracture risks have been reported to be higher and BMD lower in non-persistent patients taking a placebo compared with persistent patients in the placebo wing of an intervention study [202].

Fig. 13 Relative risk (RR) of 2-year fracture incidence (reference: <1 month of treatment) [202]



Patient education and nurse-led monitoring early in the course of treatment have been shown to improve compliance [203]. Whether monitoring by measurement of biochemical markers of bone turnover or BMD provides additional benefits has not been established [14, 15, 204]. The determinants of low persistence and compliance to treatment are not well understood. Research suggests that several factors are important, including dosing requirements and frequency, adverse events, the patient-physician relationship, and patient inability to detect improvements in an asymptomatic disease [197, 205–208]. Retrospective studies indicate that weekly dosing regimens are associated with better

persistence than daily regimens [208]. New treatments have quarterly (i.v. ibandronate), 6-monthly (denosumab), or annual (zoledronic acid) dosing. Theoretically, this type of administration should have potential to improve adherence. However, to what extent increased use of these drugs will improve adherence and lead to fewer fractures in clinical practice is currently not known. This will be an important issue to address in future studies when sufficient real world data become available.

2.5.6.1 Cost-effectiveness and adherence

Health economic modelling of anti-fracture therapies is a thoroughly researched area, and many publications on the topic are available. However, adherence is seldom included in the cost-effectiveness models. Poor adherence is commonly believed to have little impact on cost-effectiveness in clinical practice, since poor adherence affects cost as well as outcomes. Also of relevance is that with poor adherence fewer patients will be properly treated, and thus fewer fractures prevented, which is the principal goal of treatment. Cost-effectiveness analysis is also important in this context since future improvements in fracture prevention may come not only from more efficacious treatments but also through improved drug delivery and adherence [209]. Thus the prices, costs, and cost-effectiveness of these new alternatives need to be compared with the present alternatives in clinical practice.

From a health economic perspective, high adherence is particularly important when treating high-risk populations. Cost-effectiveness of treatments that potentially confer high adherence is sensitive to assumptions regarding the relation between adherence and residual effect after stopping treatment and drug-effect reductions from poor compliance.

Modelling studies of denosumab (6-monthly dosing) [143] and zoledronic acid (12-mothly dosing) [210] have indicated that improving treatment adherence is likely to be cost-effective. The health benefits of improved adherence are often partially offset by increased intervention costs that are associated with the improved drug-taking behaviour. Nonetheless, adherence is likely to be associated with added value for the health-care system because more fractures will be avoided [209, 211].

To summarise, adherence to osteoporosis treatment is sub-optimal and associated with reduced anti-fracture effectiveness in clinical practice. The treatment gap in the management of osteoporosis in Europe is partly caused by insufficient case finding, but also in part by sub-optimal treatment adherence. Besides improved case finding, improved adherence to treatment would increase treatment penetration in high-risk populations and would likely be associated with improved outcomes in clinical practice.

2.6 National guidelines and reimbursement policies for the management of osteoporosis in EU5

Recommendations from national guidelines from France, Germany, Italy, Spain and the UK are summarized below and in Table 20. Guidelines for Sweden are currently being redrafted [70].

Table 20 Summary of the main features of guidelines in EU5

Country	Date	Scope	Risk assessment	Population-based screening	Criteria for treatment	Economic analysis linked	Reference
France	2006 Updated 2008	Postmenopausal women, men and GIOP	BMD, age, previous fracture, CRFs	No	Vertebral or hip fracture + T-score ≤−1 or BMD ≤−2.5 + CRFs or T-score ≤−3	No	AFSSAPS, 2006 [212]
Germany	2006 Updated 2009	Postmenopausal women, men	BMD, age, previous fracture, CRFs	Women aged over 70 and men aged over 80 years*	Vertebral fracture + T-score ≤−2 or 10-year probability >30%	No	DVO, 2006 & 2011 [213, 214]
Italy	2009	Postmenopausal women, men and GIOP	BMD, age, previous fracture, CRFs	Women aged over 65 years*	Not explicitly stated	No	Adami et al, 2009 [215]
Spain	2008	Postmenopausal women, men and GIOP	BMD, age, previous fracture, CRFs	No	Not explicitly stated	No	González Macías et al, 2008 [216]
UK (NICE)	2008 Updated 2011	Postmenopausal women with osteoporosis	BMD, age, previous fracture, other CRFs	No	Women aged >75 with a fragility fracture. Women aged <75 years must have T-score ≤−2.5 or lower	Yes	NICE, 2008 & 2011 [217] [218] [219]
UK (NOGG)	2008	Postmenopausal women, older men, GIOP	FRAX	No	Age-dependent 10-year fracture probability	Yes	Compston et al, 2009 [67]

GIOP - glucocorticoid-induced osteoporosis

CRF – clinical risk factor

BMD – bone mineral density

* DXA recommended but no official screening programme

2.6.1 French guidelines

French national guidelines issued in 2006 address the prevention of fractures in postmenopausal women, men, and men and women taking oral glucocorticoids [212]. A case-finding approach is used; bone densitometry being recommended in individuals with risk factors for fracture. Criteria for pharmacological intervention are based on previous fracture history, T-scores, and CRFs. In individuals without a previous history of fracture, a BMD T-score of ≤−2.5 SD with other risk factors or a BMD T-score of ≤−3 SD are regarded as an indication for treatment. In those with a history of fracture, treatment is recommended in individuals with a T-score ≤−2.5 SD, or in the case of vertebral or hip fractures, a T-score ≤−1 SD. Alendronate, risedronate and strontium ranelate are first line options, with raloxifene, etidronate, ibandronate and parathyroid hormone peptides as alternative options. In patients taking oral glucocorticoids (≥7.5 mg daily for at least 3 months) treatment is recommended in all postmenopausal women with a history of fracture. In the absence of a previous fracture, treatment is recommended in individuals with a BMD T-score of ≤−1.5 SD.

An update in 2008–9 includes a discussion of FRAX but does not explicitly recommend its use, nor are treatment recommendations based on 10-year fracture probability although, as in the previous version, the utility of CRFs in fracture risk assessment is recognised. An update of the guidelines, scheduled in 2010–2011, will include new treatments (zoledronic acid and denosumab), provide a consensus on the potential role of FRAX or other algorithms incorporating risk factors for fracture risk prediction, and provide guidance on monitoring of therapy and optimal duration of treatment. This update will be produced by the French Society of Rheumatology and Groupe de Recherche et d'Informations sur les Ostéoporoses (GRIO).

DXA is reimbursed for men and women with a fragility fracture, those taking oral glucocorticoids at a dose of ≥7.5 mg daily for 3 months or longer, and for patients with some forms of secondary osteoporosis. Additionally, in postmenopausal women, reimbursement is available for those with a parental history of hip fracture, a BMI ≤19 kg/m^2, menopause before the age of 40 years and past use of glucocorticoids (≥7.5 mg/day prednisolone for 3 months or more). Treatment is reimbursed in men and women with fragility fracture, postmenopausal women with a BMD T-score ≤−3 SD or in those with a BMD T-score ≤−2.5 SD plus at least two other risk factors (age ≥60 years, current glucocorticoid therapy, parental hip fracture or menopause before age 40 years).

2.6.2 German guidelines

German national guidelines issued in 2006 and subsequently updated in 2010 address the prevention, diagnosis and therapy of osteoporosis in adult women and men [213, 214]. Assessment of BMD using DXA is recommended in women aged ≥70 years and men aged ≥80 years. In women younger than 70 years and men younger than 80 years a case-finding approach using fracture ± CRFs is used to select individuals for diagnostic assessment.

Treatment is recommended in individuals with a single moderate or severe vertebral fracture or more than one vertebral fracture if the BMD T-score is <−2 SD, and in individuals with an estimated 10-year fracture probability of vertebral or hip fracture of ≥30% (equivalent to a 15% 10-year probability for major osteoporotic fractures) and a BMD T-score of ≤−2 SD. A table containing T-scores that on average correspond to a 30% fracture probability in men and women at different ages is provided, with the caveat that these thresholds may be lowered in the presence of CRFs.

No first-line treatment options are explicitly recommended; however, it is stated that alendronate, oestrogen, ibandronate, risedronate, strontium ranelate and teriparatide have all been shown to reduce non-vertebral fracture in postmenopausal women (hip fracture is not considered separately). Alendronate, risedronate, teriparatide and zoledronic acid are mentioned as possible treatments for men.

Reimbursement for DXA is currently restricted to patients with a fragility fracture. There are no formal restrictions concerning treatment reimbursement, but in practice limited budgets for medications may make physicians reluctant to prescribe treatment. In many districts physicians are obliged to prescribe generic alendronate for a certain percentage of patients.

2.6.3 Italian guidelines

Italian guidelines for the diagnosis, prevention and treatment of osteoporosis were published in 2009 [215]. Postmenopausal women, men, and individuals taking glucocorticoids are included in the scope of the guidelines. Bone densitometry is recommended in all women above 65 years of age, whereas in younger postmenopausal women and in men bone densitometry is recommended only in those with CRFs. The guidelines recognise FRAX as a tool for estimating fracture probability but provide an alternative algorithm for estimating 10-year probability of hip fracture and of clinical fracture. They suggest that pharmacological intervention should be reserved for those in whom the risk of fracture is “rather high” but do not specify intervention thresholds. In the context of prevention, the guidelines state that use of pharmacological agents in individuals with a BMD T-score ≥−2.5 SD is usually not justified.

First-line and second-line therapeutic options are not explicitly stated but the wider spectrum of anti-fracture efficacy across spine, non-vertebral sites and hip of alendro-

nate, risedronate, zoledronic acid, HRT and strontium ranelate, is acknowledged as compared to other interventions.

Criteria for reimbursement of treatment with bisphosphonates, strontium ranelate and raloxifene are a previous hip fracture, previous moderate or severe vertebral fracture, glucocorticoid therapy ≥5 mg daily prednisolone or equivalent for ≥3 months, hip BMD T-score ≤−4.0 SD, or hip BMD T-score ≤−3.0 SD plus at least one other risk factor (wrist fracture, low dose glucocorticoid therapy, rheumatoid arthritis, early menopause, low body weight, or family history of fracture).

2.6.4 Spanish guidelines

Spanish national guidelines were published in 2008 [216]. They cover postmenopausal women, men and glucocorticoid-treated individuals and recommend a case-finding approach to select individuals for bone densitometry, based on the presence of CRFs. Reference is made to FRAX but its use in estimating fracture probability is not explicitly recommended, although the use of CRFs to improve fracture risk prediction is discussed.

Alendronate and risedronate are recommended as first-line agents, although teriparatide is also considered a first-line agent in patients with more than two vertebral fractures. Alendronate and risedronate are also recommended as first-line agents in men and individuals taking glucocorticoids. Intervention thresholds for individuals other than those with vertebral or hip fracture are not defined.

Reimbursement is unrestricted for both DXA and treatment, although the accessibility of DXA in parts of the country is poor.

2.6.5 UK guidelines

The National Institute of Health and Clinical Excellence (NICE) issued guidance for the primary and secondary prevention of osteoporotic fractures in postmenopausal women in October 2008. This was amended, although without significant change, in January 2011 as a result of a High Court Appeal that ruled against NICE [217, 218]. NICE has recently issued separate guidance for the use of denosumab in postmenopausal women [219]. A case-finding approach is used to identify women at risk of fracture and, although the FRAX risk factors are used in the economic model, intervention thresholds are not expressed as 10-year fracture probability but rather a combination of BMD, age and selected CRFs. Women aged over 75 years with a fragility fracture may be treated without BMD measurement with alendronate, but younger postmenopausal women with one or more fractures may only receive treatment if the BMD T-score is −2.5 SD or lower. Women who cannot tolerate alendronate have to satisfy more stringent disease criteria (based on BMD and CRFs) or become older before receiving other treatments. For women who have not had a fracture, a T-score of ≤−2.5 SD is a necessary prerequisite for treatment except in those aged 75 years or more who have two or more CRFs. Again, more stringent treatment thresholds are stipulated for women who cannot tolerate oral alendronate. The NICE appraisals have been subject to much criticism [220].

In 2008, NOGG developed guidelines for osteoporosis to address the omission from NICE guidance of glucocorticoid-induced osteoporosis, men with osteoporosis, newer interventions such as ibandronate, zoledronic acid and denosumab, and women with a T-score ≥−2.5 SD [67]. NOGG recommends a case-finding approach incorporating FRAX, with or without BMD. Intervention thresholds are age-specific and based on the risk of subsequent fracture in a woman presenting with an incident fragility fracture, irrespective of BMD. Alendronate is the recommended first-line option, but other treatments (excepting PTH peptides) are all regarded as second-line options and do not require more stringent disease criteria as in the NICE guidance.

In the National Health Service, access to DXA and treatment is determined primarily by NICE guidance and both are free of charge provided that the criteria set out in the guidance are satisfied.

In all the guidelines some case-finding approach is suggested for patient identification. However, they are all varying in terms of what risk factors to acknowledge, how the fracture risk should be assessed and how BMD measurements should be used. In all countries age, BMD and prior fragility fracture is recognised as important risk factors. Different variations of intervention thresholds defined as absolute fracture risk is used in Germany, Italy and the UK (NOGG guidelines). The FRAX tool is considered but not specifically incorporated in the suggested case-finding recommendations in the French, Italian and Spanish guidelines. In the UK NICE guidelines, FRAX risk factors are used in the cost-effectiveness analysis but are not used for determining intervention thresholds. The UK NOGG guidelines suggest a case-finding approach based on FRAX-estimated intervention thresholds.

It is only in the UK guidelines that alendronate is the sole recommended first-line option. In the other countries other drugs are also considered as first line treatments. This is because the UK guidelines have also considered the cost-effectiveness of the treatments when developing the guidelines and the price of alendronate is particularly low in the UK. The guidelines in the other countries have mainly considered

the clinical profiles of the drugs when defining the treatment line.

2.6.6 Compliance to guidelines

The Prospective Observational Study Investigating Bone Loss Experience in Europe (POSSIBLE EU) is a longitudinal, non-interventional cohort study with the objective to examine the use of osteoporosis medications in EU5 [221]. The POSSIBLE EU included 3,402 women that either were receiving or starting osteoporosis treatment. Information regarding demographics, bone diagnosis (e.g. DXA), risk factors, co-morbidities and concomitant medication was collected at baseline. Patients were followed up after one year. The data collected in POSSIBLE EU provide interesting information on how osteoporosis treatment is managed in clinical practice. An analysis of the baseline data showed that only 52% of all patients had been evaluated by DXA and 68% of these patients had osteoporosis and 32% osteopenia. 25% of all patients had no DXA and no prevalent fractures. There were also large variations between countries, for example the proportion of patients that had osteoporosis (T-score <−2.5 SD), a prior fracture and/or glucocorticoid therapy was 55% in Spain and 83% in the UK.

These are interesting findings because they imply that osteoporosis is managed somewhat differently in clinical practice compared to national guidelines. It seems that even though not specifically acknowledged and recommended in several of the guidelines, physicians in clinical practice do consider other risk factors such as parental fracture, smoking and alcohol use in the treatment decision. However, it also seems that guidelines have an impact in clinical practice. For example, the UK which has more restricted recommendations (i.e., the NICE guidelines) also have a notable higher proportion of patients that fall under a more classical definition of osteoporosis and high risk of fracture based on BMD and prior fracture.

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3 Epidemiology of osteoporosis

Summary

The objective of this chapter is to map the epidemiology of osteoporosis and its consequences in the EU5 and Sweden (EU5+). This forms the basis for estimating the burden of osteoporosis which is presented in Chapter 5 and 6. Different approaches for setting intervention thresholds (i.e. at what fracture risk is it appropriate to start treatment) are also described.

The key messages of this chapter are:

Osteoporosis and osteoporotic fractures are rare before the age of 50 years. The incidence of fractures in subsequent years rises progressively with age.

Accurate country-specific estimates of the prevalence of osteoporosis require national data on BMD in men and women aged 50 years or older.

Age-specific estimates of BMD are similar in EU5+ and the differences in mean BMD and standard deviations are relatively small with age.

Approximately 6% of all men and 21% of all women aged 50–84 years in EU5+ are estimated to have osteoporosis.

The yearly incidence of hip fracture is well documented in EU5+ and range from 0.01% for women aged 50–54 in Spain to 4.77% for women aged 95 or older in the UK. The corresponding estimates for men are 0.01% and 2.00%.

Country-specific incidence data for forearm, clinical vertebral, and other osteoporotic fractures are scarce, with the exception of Sweden.

The number of new fractures in 2010 was estimated at 2.35 million in the EU5 and 2.46 million when Sweden was included. Of these 67% were in women. The majority of the fractures sustained were "other" fractures (i.e., pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures) followed by hip, forearm and clinical vertebral fractures.

In the EU5, Spain was estimated to have the lowest life-time fracture probability and Sweden the highest.

Osteoporosis is associated with an increase in mortality. Studies suggest that approximately 30% of the excess mortality may be directly attributed to the fracture event.

Excess mortality after hip fracture is well described. During the first year following a hip fracture, the relative risk increase in mortality for women varies between 1.5 to >9, depending on age. Some studies have shown an increase in mortality following hospitalised vertebral fracture, whereas forearm fractures are not associated with excess mortality.

Approximately 34,000 deaths annually are caused by fractures in the EU5 and Sweden. Approximately 49% of the fracture related deaths in women are caused by hip fractures, 26 % by clinical vertebral and 25% by "other" fractures. Corresponding proportions for men are 46%, 34% and 19%, respectively.

The IOF and the WHO recommend that risk of fracture should be expressed as a short-term absolute risk, i.e., probability over a ten year interval, when assessed for intervention.

On average, more than 72% of the total female population in the studied countries has a 10-year probability of an osteoporotic fracture greater than 5%. The risk is greater than 15% for 23 % of the female population. The corresponding proportions for men are 28% and 3% above the risk of 5% and 15%, respectively.

In Europe the number of elderly is set to increase markedly and improvements in life expectancy indicate that the number of fractures will continue to rise as the population ages.
When defining intervention thresholds for osteoporosis (at what 10-year fracture probability treatment should be started) it is important to consider both clinical and health economic factors.

With regard to intervention thresholds, the suggested approach for the development of guidelines based on fracture probability is to 'translate' current practice in the light of FRAX.

The suggested method for setting the intervention thresholds using the translational approach is set the fracture risk for treatment eligibility equivalent to the risk of a women with a previous fracture (no other clinical risk factors, an average BMI and without BMD).

Available health economic studies indicate that osteoporosis treatment is cost-effective at the intervention threshold levels set by the translational approach in EU5.

3.1 Introduction

The primary objective of this chapter is to map the epidemiology of osteoporosis and its consequences in the five largest countries in the European Union;

Germany, France, the UK, Italy and Spain referred to as the EU5. In addition, information is provided for Sweden, collectively referred to as the EU5+. The reason for including Sweden in the review is that much of the data used for generation of epidemiological estimates come from Sweden. Sweden is also an example of a country with a high incidence of fractures, which can serve as a reference for other high incidence countries, in relation to the lower incidence in southern Europe. The information provided in this chapter forms the basis for estimating the burden of osteoporosis which is presented in Chapters 4 and 6.

3.2 The population at risk

Osteoporosis and osteoporotic fractures are rare before the age of 50 years. The incidence of fractures rises progressively with age thereafter. For the purposes of this report we consider the population at risk to include men and women from the age of 50 years. The populations of EU5 for 2010 are given in Table 21. In all, there are 116.7 million people aged 50 years and above in the EU5 and 54% of the population is female. Germany has the most inhabitants (32.9 million) and Spain the least (15.7 million). Estimates were based on United Nations World Population Prospects data [1].

Table 21 Population size (in thousands) in 2005 by five-year age group and sex (M = men, W = women), (medium variant), 2010 in the EU5 and Sweden

	France		UK		Germany		Italy		Spain		Sweden		EU5+	
Age	W	M	W	M	W	M	W	M	W	M	W	M	W	M
50-54	2,143	2,038	2,011	1,959	3,054	3,131	2,026	1,983	1,505	1,483	288	295	11,027	10,889
55-59	2,086	1,980	1,820	1,763	2,763	2,726	1,879	1,795	1,309	1,263	285	288	10,142	9,815
60-64	1,998	1,894	1,932	1,839	2,293	2,225	1,928	1,803	1,226	1,149	310	309	9,687	9,219
65-69	1,342	1,235	1,523	1,414	2,422	2,248	1,657	1,475	1,066	957	266	262	8,276	7,591
70-74	1,305	1,085	1,308	1,153	2,572	2,207	1,664	1,378	968	801	199	180	8,016	6,804
75-79	1,290	932	1,095	874	1,792	1,352	1,457	1,059	981	734	167	132	6,782	5,083
80-84	1,114	667	883	588	1,454	847	1,182	711	756	485	144	96	5,533	3,394
85+	1,169	487	990	440	1,447	459	1,196	506	702	328	173	83	5,677	2,303
All ages	12,447	10,318	11,562	10,030	17,797	15,195	12,989	10,710	8,513	7,200	1,832	1,645	65,140	55,098

3.2.1 Prevalence of osteoporosis

The threshold for diagnosing osteoporosis using DXA at the femoral neck is 0.577 g/cm^2 derived from the young white female population aged 20–29 years using the NHANES III reference data [2]. An accurate estimate of the prevalence of osteoporosis in any country requires national estimates of BMD in men and women aged 50 years or more. Such data are not reported here, even though regional data are available for many countries including France [3], Germany [4], the Netherlands [5, 6], the UK [7–10] and several other European countries [11]. The available data indicate that differences between countries in mean BMD and SDs are relatively small with age. For the purpose of this report we assume that the age-dependent decrease in BMD in the EU5 and Sweden is the same as that in NHANES III [2, 12]. The prevalence of osteoporosis using these criteria is shown for men and women for Sweden in Table 22.

Table 22 Prevalence of osteoporosis at the age intervals shown in Sweden using female-derived reference ranges at the femoral neck [12]

	Men		Women	
Age range (years)	% of population	Number affected (thousand)	% of population	Number affected (000)
50–54	2.5	7	6.3	17
55–59	3.5	7.6	9.6	21.1
60–64	5.8	11.4	14.3	30
65–69	7.4	14.2	20.2	43.7
70–74	7.8	14.6	27.9	63
75–79	10.3	13.7	37.5	68.3
80–84	16.6	14.7	47.2	67.8
50–84	6.3	83.2	21.2	310.9

Approximately 6% of men and 21% of women aged 50–84 years are classified as having osteoporosis. The

prevalence of osteoporosis in men over the age of 50 years is three times less than in women – comparable to the difference in lifetime risk of an osteoporotic fracture in men and women [12]. The number of men and women with osteoporosis using these criteria is shown for men and women in EU5 in Table 23. More than 15 million men and women aged more than 50 years have osteoporosis in the EU5.

Table 23 Number (in thousands) of men and women with osteoporosis according to age in the EU5 using female-derived reference ranges at the femoral neck

	France		UK		Germany		Italy		Spain		EU5	
Age group	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
50-54	135	51	127	49	192	78	128	50	95	37	695	272
55-59	200	69	175	62	265	95	180	63	126	44	974	344
60-64	286	110	276	107	328	129	276	105	175	67	1,385	535
65-69	271	91	308	105	489	166	335	109	215	71	1,672	562
70-74	364	85	365	90	718	172	464	107	270	62	2,236	531
75-79	484	96	411	90	672	139	546	109	368	76	2,543	524
80-84	526	111	417	98	686	141	558	118	357	81	2,612	563
50-84	2,266	613	2,079	601	3,350	920	2,487	661	1,606	438	12,117	3,331

3.2.2 Prevalence of osteopenia

Provision is made by the WHO for the description of osteopenia, but osteopenia should not be considered a disease category. This is intended more for descriptive purposes for the epidemiology of osteoporosis rather than as a diagnostic criterion. Also, the identification of osteopenia will capture the majority of individuals who will develop osteoporosis in the next 10 years. The prevalence of osteopenia using these criteria is shown for men and women for Sweden in Table 24.

Table 24 Prevalence of osteopenia at the age intervals shown in Sweden using female-derived reference ranges at the femoral neck [12]

	Men		Women	
Age range (years)	% of population	Number affected (000)	% of population	Number affected (000)
50–54	23.0	66.4	39.1	105.7
55–59	26.0	57.0	46.8	103.1
60–64	28.4	55.8	50.5	106.0
65–69	31.0	59.4	53.6	115.9
70–74	35.7	66.6	56.1	126.7
75–79	40.1	53.4	53.2	96.9
80–84	40.9	36.2	46.7	67.1
50–84	30.4	394.8	49.1	721.3

The prevalence of osteopenia was, as expected, higher than that of osteoporosis at all ages (Fig. 14) but does not increase markedly with age. Thus the ratio of individuals with osteopenia to those with osteoporosis varies with age. For example, in women aged 50–54 years, the number of individuals with osteopenia was 6-fold higher than the number with osteoporosis. In the age range 80–84 years, the number with either diagnosis was approximately equal. As can be seen in Fig. 14 more than 90% of women and more than 55% of men in the age group 80–84 have osteoporosis or osteopenia. The estimated number of men and women in the EU5 with osteopenia, when using these criteria, is shown in Table 25 with a total of approximately 45 million men and women.

Fig. 14 Prevalence of osteoporosis (T-score of −2.5 SD or less) and osteopenia (T-score between −1 and −2.5) using female-derived reference ranges at the femoral neck

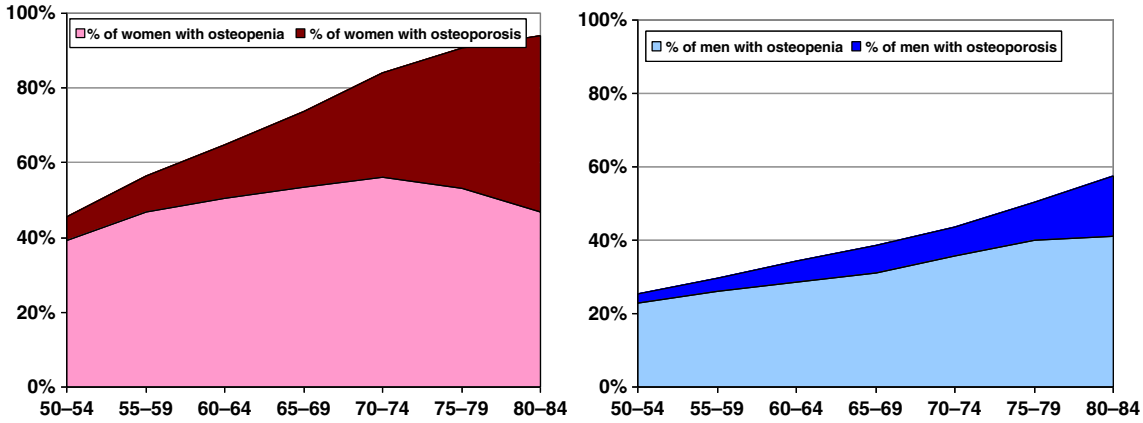


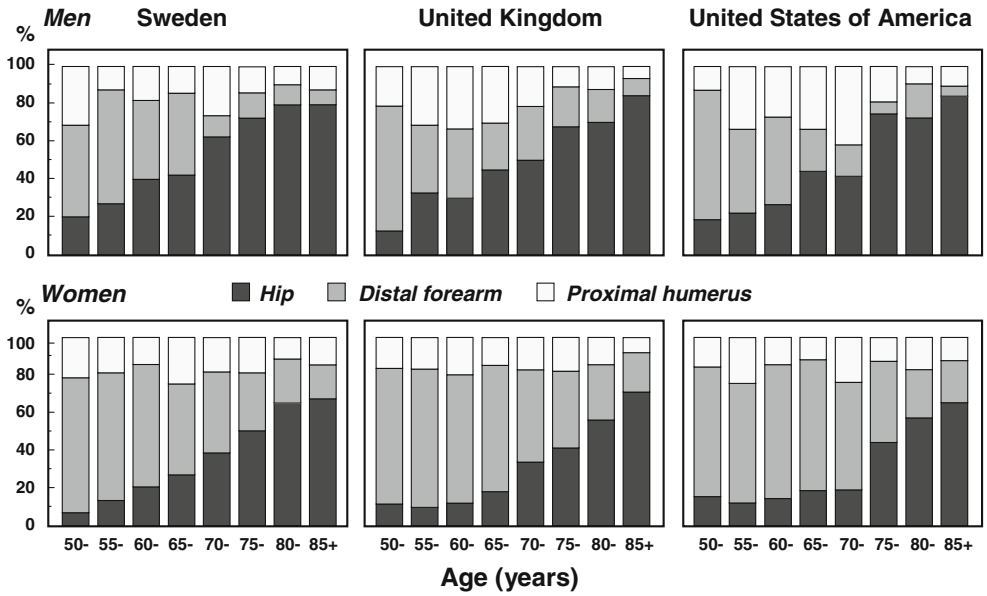
Table 25 Number (in thousands) of men and women with osteopenia (low bone mass) in the EU5 according to age using female-derived reference ranges at the femoral neck

	France		UK		Germany		Italy		Spain		EU5	
Age group	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
50-54	838	469	786	451	1,194	720	792	456	588	341	4,312	2,504
55-59	976	515	852	458	1,293	709	879	467	613	328	4,746	2,552
60-64	1,009	538	976	522	1,158	632	974	512	619	326	4,892	2,618
65-69	719	383	816	438	1,298	697	888	457	571	297	4,436	2,353
70-74	732	387	734	412	1,443	788	934	492	543	286	4,497	2,429
75-79	686	374	583	350	953	542	775	425	522	294	3,608	2,038
80-84	520	273	412	240	679	346	552	291	353	198	2,584	1,388
50-84	5,481	2,938	5,159	2,872	8,019	4,434	5,794	3,099	3,810	2,071	29,075	15,883

3.3 Incidence of fracture

Whereas patients with hip fractures are admitted to hospital and can be captured through hospital statistics and other health care agencies, patients with clinical spine, forearm and proximal humerus are commonly managed as outpatients and not all are possible to identify in the hospital databases. Estimates of the number of hip fracture were available for all included countries, but information on other fractures was incomplete. Where relevant, the incidence of other osteoporotic fractures was imputed from the hip fracture incidence from the relevant country, using the relationship between hip fracture incidence and incidence of fractures in other sites in Sweden (Malmö) [13]. This assumes that the ratio of hip fracture incidence to the age- and sex-specific incidence of other index fractures is similar in the EU5 as found in Malmö, Sweden. The assumption, used in the development of some FRAX models [14] appears to hold true for countries where this has been tested. Examples are given in Fig. 15 [15].

Fig. 15 Pattern of common osteoporotic fractures expressed as a proportion (%) of the total in the US, Sweden and the UK [15]



3.3.1 Incidence of hip fracture

Hip fracture risks for Germany were based on the only national estimate available [16]. These data have been used to populate the FRAX model for Germany. Several regional estimates of hip fracture are available for the UK. For hip fracture rates in the UK, we used the data from Singer et al. [17], based on a population in Edinburgh. This was preferred to the data of Johansen et al. [18] from Cardiff, since there were more fractures analysed (15,293 vs. 6,467). Hip fracture rates of the series from Singer were midway between the estimate of Johansen and the General Practice Research Database (GPRD) [19], but were broadly comparable. Overall, the differences in estimated risk between these studies were less than those found between other countries [20]. The estimate by Singer et al. has been widely used by others to estimate the burden of disease and for health economic modelling [21–27].

For Spain, we used mean values of four regional estimates [20, 28–30]. These data have been used to populate the FRAX model for Spain and subsequent regional estimates have shown similar fracture rates [31].

For France, we used an unpublished national survey [32] that was used to build the FRAX model for France. The study population included men and women aged 50 years and older living in France in 2004. Census data (2004) were obtained from the French official INSEE (Institut National de la Statistique et des Etudes Economiques) [33]. The claims data came from the French PMSI (Programme de Médicalisation des Systèmes d'Information), a system equivalent to the Diagnosis-Related Groups (DRG). In a burden of disease study, Maravic et al. [34] provided age-aggregated estimates based on national claims data for 2001 but did not avoid double counting since personal identifiers were not available at that time. A more recent national study provided essentially similar data but too broad age categories for our purpose [35]. National data were preferred to previous studies based on regional estimates, one from Picardy [36] and the MEDOS study in the regions of Paris and Toulouse [20] which were undertaken more than 20 years ago. In the Rhone-Alpes area, hip fracture incidence has been documented in women over the period 2001 to 2004 [37]. The three regional studies [20, 34, 36] gave lower estimates than the present study. Thus, from the previous studies of incidence [20, 36], the lifetime probability of hip fracture from the age of 50 years was given as 3.6% and 12.7% in men and women, respectively [38], whilst the estimate from the present study was approximately 50% higher (5.6% and 18.5%, respectively). Reasons for the discrepancies may be due to regional differences in hip fracture risk that have been reported for several countries [38–41] including France [20, 34, 36], errors of accuracy or secular changes in hip fracture (or mortality) risks [42].

For Italy, we used regional estimates (Parma 1989, Sienna 1989, Rome 1989) as given in Kanis et al. [38]. This was supplemented with two additional regional surveys from Verona and Friuli-Venezia [43]. The mean of age- and sex-specific incidence was calculated.

Swedish data were available from Malmö for all included fracture sites [13]. Hip fracture incidence for the EU5 and Sweden is shown in Table 26. Hip fracture incidence

increased exponentially with age in women as well as in men. As expected, lower rates were seen in men compared to women. There was some heterogeneity in fracture rates between the included countries. Spain stands out as the country with lowest incidence rates in both women and men - consistent with the observations of differing hip fracture rates within Europe [20, 44, 45]. Differences in incidence among men and women within a country may be accounted for by differences in femoral neck BMD, but do not explain the large differences between countries [38]. Hip fracture rates were smoothed assuming an exponential increase in incidence with age.

Table 26 Hip fracture incidence (per 100,000) by age in men and women from the EU5 and Sweden

	Age intervals (years)									
Country	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
Men										
France	32	43	58	82	145	302	646	1,139	1,930	2,694*
Germany	54.5[d]		89.2	119.5	214	379.5	785.9	1,509.4	2,024*	
Italy	40	40	50	120	240	420	730	1,720	2,130 *	
Spain	10	21.8	56.2	52.2	136.2	225.6	494.8	1,022*		
Sweden	88	88	76	189	304	629	1,474	1,807	1,852	
UK	22	39	69	121	213	374	657	1,115	2,003*	
Women										
France	26	42	75	129	277	621	1,380	2,237	3,379	3,719*
Germany	45.5[d]		92.5	158.5	363.6	789.5	1,533.5	2,735.7	3,557.2*	
Italy	40	60	110	200	370	820	1,470	2,610	3,070 *	
Spain	14.3	29.8	53.5	90.1	238.4	483.7	1,108.3	2,108.8*		
Sweden	55	56	192	315	556	1392	2,348	4,290	3,998	3,958
UK	30	57	107	201	379	713	1,344	2,532	4,770*	

* ≥age
[d] decade

3.3.2 Incidence of forearm fracture

Incidence of forearm fractures was available for the UK and we used the same source as that for hip fracture rate [17]. The majority of forearm fractures are treated in hospital outpatient departments [46] and are therefore seldom captured in registries. For this reason, no data were available for the other EU5 countries. As detailed above, forearm fracture rates were imputed from the relationship between hip fracture incidence and forearm fracture in Sweden. The incidence of forearm fractures in EU5 and Sweden is shown in Table 27.

Table 27 Forearm fracture incidence (per 10,000) by age and sex in the EU5 and Sweden

Country	Age intervals (years)								
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90–94
Men									
France	4	8	11	11	4	8	11	22	40
Germany	6	20	10	24	8	11	17	22	28
Italy	5	7	10	17	7	12	12	33	44
Spain	0	3	8	8	7	5	8	12	19
Sweden	12	15	20	20	12	21	28	35	41
UK	12	8	6	6	12	12	14	15	25
Women									
France	18	35	22	29	45	49	77	84	101
Germany	23	59	41	59	78	65	77	96	112
Italy	27	50	32	44	61	65	82	98	92
Spain	5	18	17	18	32	38	54	62	65
Sweden	43	50	62	78	96	110	128	146	164
UK	21	33	43	53	65	70	73	90	95

3.3.3 Incidence of vertebral fracture

Vertebral fracture may be defined in several ways. Morphometric vertebral fractures are identified as radiographic deformities. They may be symptomatic or clinically silent. Thus, not all morphometric vertebral fractures come to clinical attention and the proportion that does come to clinical attention varies between studies and between countries [19, 47, 48]. Several studies indicate that the ratio of clinical to morphometric fractures is approximately 20% in women and 40% in men [48, 49]. In the context of this report, we have preferred to estimate the incidence of clinically relevant

vertebral fracture, since these are the patients most likely to be identified for treatment. The incidence of clinically identified fractures has been studied in the UK within the GPRD [19]. The incidence is, however, very low and it is likely that the majority of fractures were not coded [50]. Indeed, reported rates of vertebral fracture vary by more than 10-fold in general practice in the UK [51]. The ratio of clinical fractures identified in the GPRD to those identified by morphometry in the UK is unrealistically low compared with other countries [52], which supports the view that the GPRD has markedly under-reported clinical vertebral fracture.

For these reasons, we imputed vertebral fracture rates from data available from Malmö in Sweden that report the incidences of hip and vertebral fractures that come to clinical attention [13]. We assumed that the ratio of the incidence of vertebral fracture and hip fractures in Malmö, Sweden would be comparable to the ratio of vertebral fracture incidence in each EU5 country (unknown) and hip fracture incidence in each EU5 country. The rates are shown in Table 28.

Table 28 Clinical vertebral fracture incidence (per 10,000) by age and sex in the EU5 and Sweden

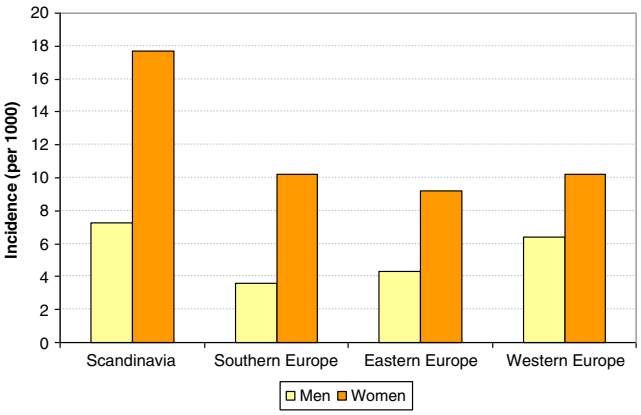
	Age intervals (years)								
Country	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94
Men									
France	7	6	18	10	24	30	40	80	151
Germany	12	10	19	17	27	36	43	82	128
Italy	9	6	16	14	40	41	45	121	166
Spain	1	3	10	8	16	22	27	45	73
Sweden	16	16	23	34	55	74	104	130	156
UK	2	7	12	14	33	34	38	72	141
Women									
France	4	10	24	33	46	70	99	114	136
Germany	8	14	14	19	40	60	78	106	127
Italy	3	18	27	34	63	112	116	120	136
Spain	2	7	8	11	25	37	54	68	83
Sweden	16	22	36	57	91	113	135	183	231
UK	10	13	12	19	50	60	72	105	142

The incidence of morphometrically-defined vertebral fractures appears to vary less between countries than the incidence of clinical fractures [52]. Results from the European Prospective Osteoporosis Study (EPOS) [52] indicate that the incidence of morphometric vertebral deformities is greater in women than in men (Table 29). The incidence increases with age but less steeply than that of hip fractures. Moreover, the international variation in the incidence of morphometric vertebral fractures is smaller than that of hip fracture (Fig. 16). Morphometrically diagnosed fractures collectively give rise to morbidity and are associated with an increased risk of future fractures. It should however be noted that they also include the fractures that come to clinical attention, which makes the burden attributable to purely sub-clinical fractures difficult to assess.

Table 29 Incidence of vertebral fracture (per 10,000) defined morphometrically in EPOS [52]

	Incidence		Relative risk
Age	Men	Women	Women vs. Men
50-54	5	36	4.1
55-59	55	55	1.0
60-64	48	95	2.0
65-69	63	123	2.0
70-74	87	179	2.1
75-79	136	293	2.2
All	57	107	1.9

Fig. 16 Age-standardised incidence of morphometrically defined fracture by region and gender from EPOS [52]



3.3.4 Incidence of proximal humeral fracture

Incidence of humeral fractures was available for the UK and we used the same source as that for hip fracture rate [17]. The majority of humeral fractures are treated in hospital out-patient departments and for this reason no data were available for the other EU5 countries. As detailed above, humeral fracture rates were imputed from the relationship between hip fracture incidence and proximal humerus fracture in Sweden. The incidence of humeral fractures in EU5 is shown in Table 30. The incidence reported for the UK is slightly lower than the imputed data in the oldest sub-group (85+years).

Table 30 Incidence of humeral fractures (per 10,000) by age and sex in the EU5 and Sweden

	Age intervals (years)							
Country	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
Men								
France	2	2	3	3	7	5	10	33
Germany	4	4	3	7	12	7	14	34
Italy	3	2	2	5	12	8	11	49
Spain	1	1	3	2	7	4	7	29
Sweden	7	3	6	9	21	18	24	51
UK	3	5	6	8	12	5	12	17
Women								
France	6	5	4	11	12	24	29	58
Germany	7	8	7	23	21	31	29	67
Italy	8	7	6	17	17	31	31	68
Spain	3	3	3	8	11	18	23	55
Sweden	12	13	13	35	38	63	59	112
UK	6	9	14	13	25	31	37	36

3.3.5 Incidence of other osteoporotic fractures

The 10-year fracture probabilities estimated by FRAX tool include fractures of the hip, clinical vertebral, forearm, and humeral fractures, but there are other fractures associated with osteoporosis that incur disability and health care costs. When calculating the burden of disease (Chapters 4 and 6) we therefore used the incidence of "other fractures" (Table 31) which includes a wider range of fracture types that is considered to be related to osteoporosis. The included fracture types were: pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures. Complete data on the incidence of other fractures were only available for Sweden [15] and the incidence of "other" fractures was imputed with the same method as used for wrist, vertebral and humeral fractures, described above. Singer et al. [17] have published UK estimates of other fractures but did not report all fracture types (e.g., rib, clavicle and pelvis fractures). Therefore, the same imputation via hip fracture incidence and Swedish risk of "other fractures" was made for the combined incidence of "other fractures" in the UK.

Table 31 Incidence of "other" fractures (per 10,000) by age and sex in the EU5 and Sweden

	Age intervals (years)							
Country	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
Men								
France	20	49	50	49	69	60	183	334
Germany	31	125	45	102	123	79	276	343
Italy	25	45	43	71	115	84	207	504
Spain	6	25	49	31	65	45	140	299
Sweden	72	82	85	129	136	248	457	521
UK	55	96	61	120	142	126	432	496
Women								
France	19	41	20	48	70	124	219	384
Germany	25	70	39	98	120	164	219	440
Italy	30	59	30	74	93	163	233	448
Spain	11	29	15	33	60	96	176	362
Sweden	49	54	78	125	187	293	459	753
UK	45	54	53	115	139	260	342	635

3.4 Number of fractures

The number of new fractures in 2010 was estimated at 2.35 million in the EU5 and 2.46 million when Sweden was included (Table 32). Of these 67% were in women. The majority of the fractures sustained were "other" fractures followed by hip, forearm and clinical vertebral fractures. About twice as many fractures were found in women than in men. Individuals 75 years of age or older sustained the majority of the vertebral and hip fractures whilst most of the forearm fractures incurred in the younger population (Table 33).

Table 32 Summary of new fractures in 2010 in women and men aged 50 years or more

	Site of fracture				
Country	Hip	Vertebral [a]	Forearm	"Other"	All sites
Women					
Sweden	14,785	10,529	13,580	31,871	70,765
Spain	29,866	18,936	24,928	64,803	138,533
France	55,658	36,691	47,647	118,903	258,899
Italy	70,323	50,602	65,943	152,721	339,590
UK	56,735	40,369	54,309	191,781	343,194
Germany	98,824	76,460	100,148	219,452	494,884
EU5	311,406	223,058	292,975	747,660	1,575,100
EU5+	326,191	233,587	306,555	779,531	1,645,865
Men					
Sweden	5,507	5,910	2,809	21,985	36,211
Spain	10,370	10,425	4,523	38,928	64,246
France	18,700	19,511	8,980	73,402	120,593
Italy	26,254	26,964	11,435	98,090	162,744
UK	22,757	25,414	12,401	130,817	191,388
Germany	33,890	38,934	19,566	146,934	239,324
EU5	111,971	121,248	56,905	488,171	778,295
EU5+	117,478	127,158	59,714	510,156	814,506
Men and women					
EU5	423,377	344,306	349,880	1,235,831	2,353,395
EU5+	443,669	360,745	366,269	1,289,687	2,460,371

[a] clinical vertebral fracture

Table 33 Estimated number of incident fractures by country and age in the population aged 50 years or more

Age intervals (years)	Sweden	Germany	France	Italy	Spain	UK	EU5+
Hip fractures							
50-74	4,697	39,282	13,091	20,852	6,607	18,451	102,980
75+	15,595	93,432	61,268	75,725	33,629	61,041	340,689
Clinical vertebral fractures							
50-74	7,551	61,506	21,793	33,232	10,615	30,806	165,503
75+	8,888	53,888	34,409	44,335	18,746	34,977	195,243
Forearm fractures							
50-74	9,837	78,701	29,763	44,126	14,344	40,357	217,128
75+	6,552	41,013	26,864	33,252	15,107	26,353	149,141
"Other" fractures							
50-74	22,159	181,308	66,240	94,967	32,365	135,635	532,674
75+	31,697	185,078	126,064	155,845	71,367	186,963	757,013

3.4.1 Prevalence of fractures

For the purposes of this report, a prevalent fracture was defined as a historical fracture in a person who was alive during the index year (i.e., 2010). Historical fractures that came to clinical attention when the person was younger than 50 years were not included. Multiple fractures in one individual were only counted as one prevalent fracture. Fractures that occurred in the index year are not counted as prevalent fractures. Data on the prevalence of hip and vertebral fractures were not available from the European literature and were therefore simulated. A micro-simulation model, programmed in TreeAge, was used to simulate the prevalence of hip and vertebral fractures from incidence data. The micro-simulation model was populated with the hip and clinical vertebral fracture incidence data described in section 2.2, normal population mortality [53], and Swedish relative risks of post-fracture mortality [54]. Age specific prevalences of hip and clinical vertebral fracture were multiplied by the age-specific population in each country [1]. Simulated prevalences are shown in Table 34. The total number of women and men with a prevalent hip or clinical vertebral fracture was estimated at 5.4 million in the EU5+ (Table 35).

Table 34 Estimated proportion of the population (%) at the age intervals shown with one or more prior hip and vertebral fracture

Prevalence of hip fracture, women				
	50-64	65-74	75-84	85+
Sweden	0.4%	2.0%	7.0%	19.1%
Spain	0.1%	0.8%	3.2%	11.3%
France	0.2%	1.1%	4.2%	13.3%
Italy	0.3%	1.6%	5.3%	15.0%
UK	0.3%	1.3%	4.8%	14.8%
Germany	0.3%	1.9%	5.4%	13.9%
Prevalence of hip fracture, men				
Sweden	0.5%	1.6%	4.6%	11.9%
Spain	0.1%	0.5%	1.7%	6.0%
France	0.2%	0.8%	2.1%	6.3%
Italy	0.3%	1.0%	2.8%	8.2%
UK	0.3%	1.1%	2.8%	8.4%
Germany	0.3%	1.2%	2.9%	7.6%
Prevalence of clinical vertebral fracture, women				
Sweden	1.0%	3.4%	8.1%	14.8%
Spain	0.3%	1.3%	3.5%	7.6%
France	0.4%	1.7%	4.4%	9.2%
Italy	0.7%	2.5%	5.5%	10.1%
UK	0.7%	2.1%	4.8%	10.3%
Germany	0.7%	3.1%	6.2%	10.1%
Prevalence clinical vertebral fracture, men				
Sweden	1.0%	2.3%	4.5%	9.1%
Spain	0.2%	0.9%	1.7%	4.1%
France	0.4%	1.2%	2.3%	5.3%
Italy	0.5%	1.5%	2.8%	6.3%
UK	0.6%	1.7%	2.7%	6.1%
Germany	0.6%	1.8%	3.0%	5.5%

Table 35 Estimated number of women and men older than 50 years with a prevalent hip or clinical vertebral fracture

	Hip fractures	Vertebral fractures
Women	67,373	75,082
Sweden		
Spain	156,806	152,973
France	293,632	286,532
Italy	386,168	387,458
UK	295,682	294,428
Germany	494,637	557,961
EU5	1,626,926	1,679,352
EU5+	1,694,299	1,754,434
Men	32,013	36,467
Sweden		
Spain	53,297	58,274
France	94,549	113,654
Italy	132,362	150,643
UK	123,849	143,824
Germany	177,109	217,012
EU5	581,165	683,407
EU5+	613,178	719,874

The proportion of past hip or vertebral fractures that engendered disability in 2010 is unknown but will likely depend on fracture site, the time since fracture, and the patient's age. The number of prior fractures varied considerably by age and the majority were found in the elderly. In total, prevalent vertebral fractures were more common than prior hip fractures because they on average will occur in younger patients, who are larger in number and with a longer life-expectancy after fracture.

3.5 Mortality due to osteoporosis and fracture

Osteoporosis is associated with an increase in mortality that is independent of a prior fracture [55–57]. Over and above this excess mortality, some fracture sites are associated with increased mortality. Although the mortality after a fracture has been shown to be higher for men compared to women [56], this difference is less marked when relating the mortality to that of the general population of the same sex [58, 59]. In health economic studies of osteoporosis it is the excess mortality that would be avoided in the absence of a fracture that is important to consider.

3.5.1 Mortality due to hip fracture

Excess mortality is well described after hip fracture. In the first year following hip fracture, mortality risk varies in women from 2.0 to greater than 10 depending upon age [56, 58, 60–62]. Several studies have shown that mortality is highest in the immediate fracture period and then decreases with time but remains higher than that of the general population [57, 62, 63]. Mortality rates after hip fracture appear to have remained constant over the past 20 years [60].

Since hip fracture patients have high co-existing morbidity, poor pre-fracture health is likely to contribute to the excess mortality. Case control studies adjusting for pre-fracture morbidity indicate that a substantial component of the death risk can be attributed to co-morbidity [64, 65]. Irrespective of the attribution, it is difficult to determine the quantum of excess mortality that would be avoided in the absence of hip fracture [66]. It has been argued that the acute increment in mortality over the first 6 months is causally related to the fracture event and that death would be avoided by avoiding the fracture. During this period, excess mortality risk has been estimated at 3.35 (95% CI = 1.50-7.47) compared to a subsequent risk of 1.30 (95% CI = 0.85-1.98) [64].

A review of case-notes by Parker and Anand [67] estimated that 33% of deaths up to 6 months after hip fracture were totally unrelated to the hip fracture, 42% possibly related and 25% directly related. These figures were not however stratified by age or sex and causality is based on opinion. Extrapolation of the data to one year suggests that 48% of all deaths may be related to the hip fracture event [68]. Notwithstanding, hip fracture resulted in more deaths than other major causes of death such as suicide and transport accidents [69].

In a large study of 160,000 hip fracture cases in 28.8 million hospital person-years the risk of death of those with a somewhat earlier hip fracture was compared to the risk of death in individuals of the same age with a later hip fracture. Two individuals of the same age, but with a different time interval between their fractures, had an equal mortality provided that the time interval between the two fractures exceeded one year. The difference in mortality of less than one year can be ascribed to causally related deaths, i.e., the death would have been avoided had the hip fracture not occurred. The analysis suggested that approximately 24% of all deaths might be causally related to the hip fracture itself [70].

In keeping with the findings mentioned above, we have assumed that 30% of the excess mortality after a hip fracture is related to the fracture itself. Age differentiated estimates of relative mortality after a hip fracture (Table 36), derived from a Swedish population study [57], were used in this report. Thereby it was implicitly assumed that the relative mortality after a hip fracture in the EU5 is comparable to that in Sweden.

3.5.2 Mortality due to vertebral fracture

Several studies have shown an increase in mortality following vertebral fracture [62, 71]. In one study, women with one or more vertebral fracture had a 1.23-fold greater age-adjusted mortality rate (95% CI = 1.10-1.37). Unlike for hip fracture, there was no acute excess documented [62, 71]. It is notable that low BMD is also associated with excess mortality [55–57], but the degree of increased mortality after vertebral fracture is greater than that expected from low BMD.

These studies used morphometric rather than clinical definitions of vertebral fracture. In contrast, other studies that examine mortality after vertebral fracture using clinical criteria have shown more marked increases in mortality [56, 57, 72]. In one study from Australia, vertebral fractures in women were associated with an age-standardised risk of 1.92 (95% CI = 1.70-2.14) [56], and in another study, the risk was more than 8-fold higher [72]. A study on clinical fractures from the UK compared mortality in patients with osteoporosis (and no fracture) to mortality in women with established vertebral osteoporosis [73]. The hazard ratio was 4.4 (95% CI = 1.85-10.6). Although absolute mortality amongst men after vertebral fracture is higher than amongst women [57], the relative mortality with fracture compared to population mortality rates ratio was similar.

Unlike for morphometric deformities, the pattern of mortality after clinical vertebral fracture is non-linear suggesting, as is the case for hip fracture, that a fraction of deaths would not have occurred in the absence of a fracture. Using the patient register for hospital admissions in Sweden 28% of all deaths associated with vertebral fracture were judged to be causally related [74]. The excess mortality compared with the general population has been shown to decline with increasing age. Thus, using a single estimate of the average relative mortality may underestimate fracture related mortality in the younger

(approximately 50-70 years) and overestimate mortality in the elderly (80+ years). For this reason we used age-differentiated estimates of relative mortality (Table 36) based on Swedish mortality data after clinical vertebral fracture [54, 57].

3.5.3 Mortality due to other osteoporotic fractures

We have assumed no increase in mortality from forearm fractures consistent with published surveys [56, 57, 62, 72]. For "other" fractures, we assumed a relative mortality of 1.22 [15, 54, 75].

3.5.4 Mortality estimates for the EU5

Most data relating to mortality associated with fracture are derived from outside the EU5. For the purposes of this report we assumed that the relative risk of death was similar in EU5 countries and comparable to Sweden [57, 58, 76], though the absolute risk of death will vary according to mortality rates in each of the EU5 countries. The excess mortality from fracture expressed in relative risks (Table 36) was multiplied by general population mortality to estimate absolute mortality the year after fracture in each analysed country.

Table 36 Relative risk of death 1st year after fracture relative to normal population[a] *(derived from [57])*

Age	Women		Men	
	Hip fracture	Clinical vertebral fracture	Hip fracture	Clinical vertebral fracture
50	9.5	12.1	15.0	17.8
55	8.4	10.1	11.7	13.2
60	7.9	9.0	9.1	9.7
65	6.6	7.4	7.1	7.2
70	5.8	6.0	5.9	5.6
75	4.5	4.4	4.7	4.3
80	3.0	2.8	3.6	3.1
85	2.3	1.9	3.0	2.5
90	1.6	1.4	2.8	2.1

[a] *Not adjusted for comorbidities*

3.5.5 Deaths due to fractures

Using the data for mortality and the estimated number of incident fractures allows the estimation of deaths due to fractures. It was conservatively assumed that fractures were only associated with mortality during the first year after fracture and that 30% of the excess mortality (Table 36) was caused by the fracture itself. Even though the mortality relative to the normal population decreases with age (Table 36), the absolute mortality in women caused by fractures was estimated to increase from 4-7 deaths/1,000 hip fractures at age 50 years to 21–31 deaths/1,000 hip fractures at age 90 years (Table 37). The number of causally related deaths per 1,000 hip fractures in men was generally higher than for women. This is caused by higher age-specific excess mortality and underlying normal mortality in men compared with women.

Table 37 The incidence by age of causally related deaths the first year after hip fracture/1,000 fractures for the EU5 and Sweden

Women						
Age	Germany	UK	Spain	France	Italy	Sweden
50	6	7	5	7	4	4
55	8	8	5	7	6	6
60	10	11	8	10	9	9
65	12	15	10	10	11	12
70	18	22	14	14	15	17
75	25	29	20	18	20	19
80	28	29	23	19	23	21
85	35	34	31	26	29	27
90	31	27	27	21	26	25
Men						
Age	Germany	UK	Spain	France	Italy	Sweden
50	19	16	18	23	12	10
55	23	19	20	25	16	15
60	25	22	25	26	20	16
65	29	27	29	26	24	21
70	37	36	34	32	31	27
75	47	46	42	39	42	35
80	54	56	50	48	51	43
85	72	72	67	63	66	63
90	109	103	99	88	102	100

When combining the number of incident fractures (Table 33) with the causally related excess mortality it was estimated that approximately 34,000 deaths annually are caused by fractures in the EU5 and Sweden (Fig. 17 and Table 38). As can be seen in Fig. 18 approximately 49% of the fracture related deaths in women are caused by hip fractures, 26 % by clinical vertebral and 25% by "other" fractures. Corresponding proportions for men are 46%, 34% and 19%, respectively. Even though about two-thirds of all fractures occur in women it was estimated that only half of the attributable deaths occur in women. The reasons relate to the higher general population mortality in men and the higher relative risk of death after fracture in men compared with women (Table 36).

Fig. 17 Causally related deaths within the first year after fracture in 2010 (women and men combined)

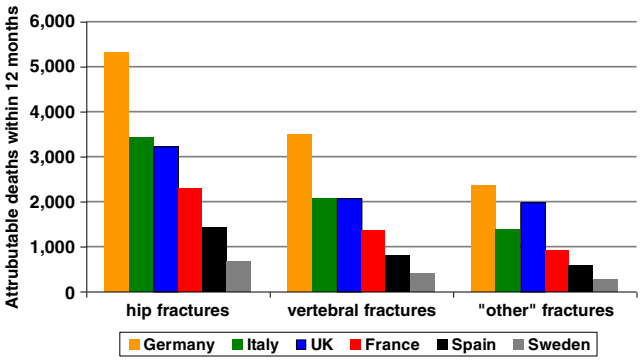
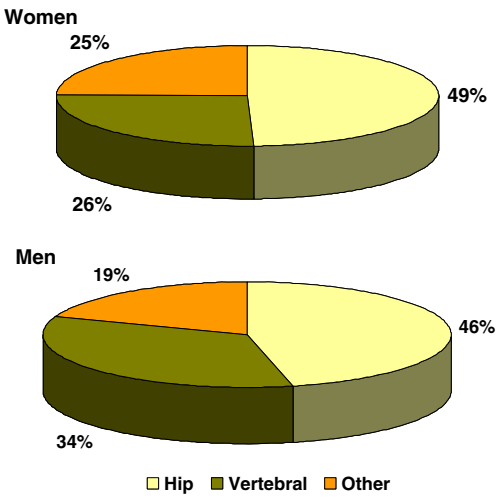


Table 38 Causally related deaths within the first year after fracture in 2010

	Deaths caused by hip fractures	Deaths caused by vertebral fractures	Deaths caused by "other" fractures	Total
Women				
Germany	2914	1620	1356	5890
UK	1635	879	1109	3623
Spain	753	335	348	1436
France	1164	565	514	2244
Italy	1708	882	782	3372
Sweden	346	179	158	683
EU5+	8520	4460	4267	17247
Men				
Germany	2416	1892	999	5307
UK	1582	1199	864	3645
Spain	679	467	243	1390
France	1129	816	419	2365
Italy	1726	1190	617	3534
Sweden	337	240	131	708
EU5+	7871	5804	3273	16948

Fig. 18 The proportion (%) of deaths due to fracture by site in men and women from the EU5 and Sweden in 2010



3.6 The probability of osteoporotic fracture and setting the threshold for intervention

The probability of fracture at any given age depends upon the hazard of death as well as the hazard of fracture. Fracture probability is not to be confused with incidence since it defines the probability of fracture over a longer time frame (e.g., 10 years or lifetime) and incorporates both fracture risk and mortality. The probability is further an estimate of the risk of sustaining a first fracture at a given site whilst the incidence is the number of fractures occurring during the same defined time interval. In general, remaining lifetime fracture probability decreases with age especially after the age of 70 years or so since the risk of death with age outstrips the increasing incidence of fracture with age. The remaining lifetime probability of fracture at the age of 50 is shown in Table 39. Spain has the lowest estimated fracture risks with lifetime probability of major osteoporotic fracture of 9% in men and 25.5% in women from the age of 50 years. Sweden has the highest estimated lifetime probability; 25.5% and 49.1% from the age of 50 years for men and women, respectively.

Table 39 Remaining lifetime probability (%) of a hip and major osteoporotic fracture in men and women aged 50 years from the EU5 countries and Sweden

	Germany	UK	Spain	France	Italy	Sweden
Men						
Hip fracture	5.3	4.8	3.9	5.6	6.1	12.7
Major osteoporotic fracture*	12.9	12.8	9.0	12.2	13.6	25.5
Women						
Hip fracture	14.0	13.7	12.0	18.6	16.4	24.9
Major osteoporotic fracture*	31.4	36	25.5	35.9	35.7	49.1

*Major osteoporotic fracture includes fractures of the hip, spine, wrist, and proximal humerus

Estimates of lifetime probability are of value in considering the burden of osteoporosis in the community and for estimating the risk reduction from interventions to reduce future risk. For several reasons they are less relevant for assessing risk of individuals in whom treatment might be envisaged [77] so that the IOF and the WHO recommend that risk of fracture should be expressed as a probability over a ten year interval [78]. The period of ten years covers the likely duration of treatment and the benefits that may continue once treatment is stopped.

A major advantage of using fracture probability is that it standardises the output from the multiple techniques and

sites used for assessment and also permits the presence or absence of risk factors other than BMD to be incorporated as a single metric. As reviewed in Chapter 2, FRAX (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture. Fig. 19 and Fig. 20 show the 10-year probability of hip fracture or a major osteoporotic fracture (clinical spine, hip, forearm and humerus fracture) for several clinical scenarios in the EU5 countries. For hip fracture probability, the lowest rates are in Spain, followed by France, Germany, the UK, Italy and Sweden. For the probability of a major fracture the rank order from the lowest is Spain, France, Germany, Italy, the UK and Sweden.

Fig. 19 Ten-year probability of a major osteoporotic fracture (%) in women aged 65 years (BMI = 25 kg/m^2) in A, the absence of clinical risk factors or BMD, B, a prior fragility fracture, and C, a prior fragility fracture and a femoral neck T-score of −2.5 SD from the EU5 countries. [FRAX v 3.1]

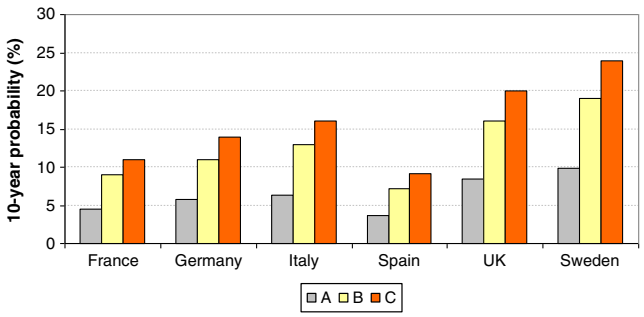
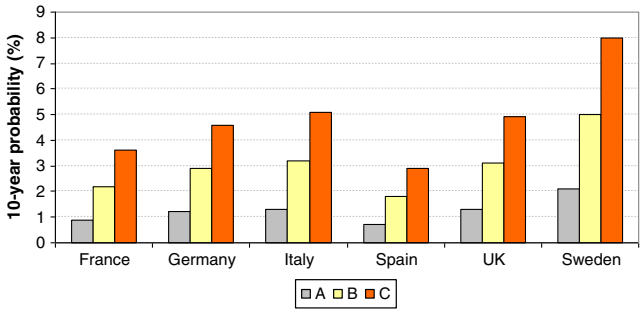


Fig. 20 Ten-year probability of a hip fracture (%) in women aged 65 years (BMI = 25 kg/m^2) in A, the absence of clinical risk factors or BMD, B, a prior fragility fracture, and C, a prior fragility fracture and a femoral neck T-score of −2.5 SD from the EU5 countries. [FRAX v 3.1]



The proportion of the population aged 50 years or more in the EU5 and Sweden above a certain probability of a major osteoporotic fracture is given by gender in Table 40. The proportion of the population above a given threshold varied among EU5 countries, and was greatest for the UK and lowest for Spain. For example, 29% of women from the UK are estimated to have a probability that exceeds 15%, whereas the corresponding proportion in Spain was less than half (13%). Intermediate values were noted for France, Germany and Italy (21, 22 and 25%, respectively). The proportions in Sweden were higher than in any of the EU5 countries, for example 42% of women from Sweden are estimated to have a probability that exceeds 15%. As expected, the proportion of men above any given threshold was much lower than that for women.

Table 40 The proportion of the population (%) aged 50 years or more in the EU5 and Sweden above a certain probability of osteoporotic fracture

	Probability of major osteoporotic fracture						Population
	> 5%	> 10%	> 15%	> 20%	> 25%	> 30%	size (000)
Men							
France	22.6	7.1	3.0	1.4	0.7	0.4	9,463
Germany	30.3	8.3	3.1	1.4	0.7	0.4	13,921
Italy	31.3	10.8	4.7	2.3	1.2	0.7	10,013
Spain	16.0	4.1	1.5	0.6	0.3	0.2	6,506
UK	29.7	7.9	2.8	1.2	0.5	0.3	9,416
Sweden	50.5	20.4	9.6	5.1	2.9	1.7	1,562
Women							
France	62.6	34.1	20.9	13.4	8.9	6.0	11,442
Germany	72.5	38.0	21.6	13.0	8.1	5.1	16,847
Italy	80.2	43.2	24.6	14.8	9.3	6.0	12,267
Spain	51.3	24.6	13.3	7.7	4.6	2.8	7,781
UK	86.3	50.4	28.9	17.4	10.8	6.9	10,995
Sweden	91.3	62.2	41.7	28.4	19.8	13.9	1,769

The number of individuals in the EU5+Sweden above a given probability of a major osteoporotic fracture is shown by gender in Fig. 21 and Fig. 22 (data also shown in Table 41). More than 44 million (>72%) women, 50 years and older, have a ten year probability of a major osteoporotic fracture above 5% in the EU5 and Sweden. 14 million (23%) women have probabilities above 15%. About 14 million (28%) and 1.7 million (3%) men have probabilities above 5% and 15%, respectively.

Fig. 21 Number of women (in thousands), 50 years and older, in EU5 and Sweden above given probabilities of a major osteoporotic fracture

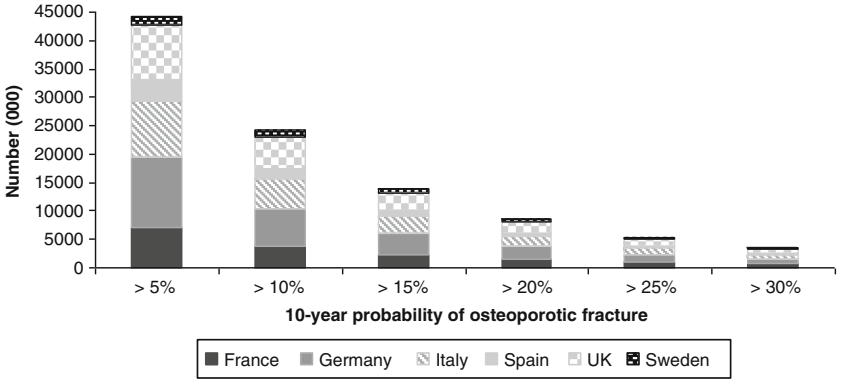


Fig. 22 Number of men (in thousands), 50 years and older, in EU5 and Sweden above certain probabilities of a major osteoporotic fracture

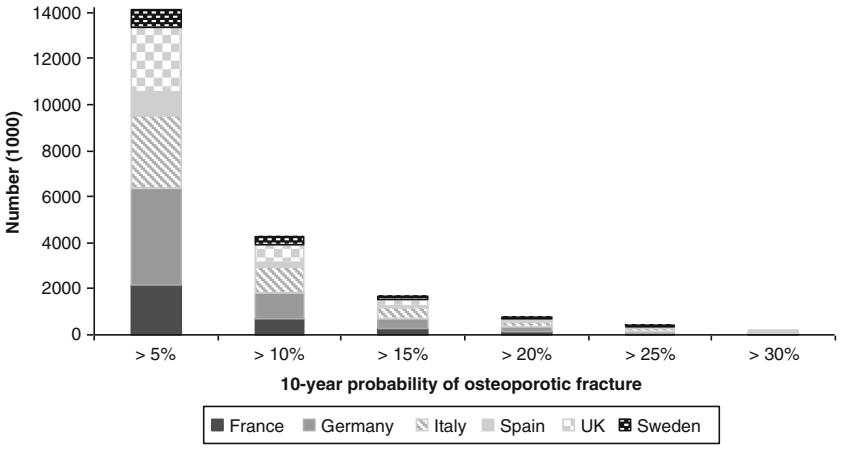


Table 41 Number of men and women (in thousands), 50 years and older, 5932 in EU5 and Sweden above given probabilities of a major 5933 osteoporotic fracture

	Probability of major osteoporotic fracture					
	> 5%	> 10%	> 15%	> 20%	> 25%	> 30%
Men						
France	2,139	672	284	132	66	38
Germany	4,218	1,155	432	195	97	56
Italy	3,134	1,081	471	230	120	70
Spain	1,041	267	98	39	20	13
UK	2,797	744	264	113	47	28
Sweden	789	319	150	80	45	27
EU5+	14,117	4,238	1,697	789	396	231
Women						
France	7,163	3,902	2,391	1,533	1,018	687
Germany	12,214	6,402	3,639	2,190	1,365	859
Italy	9,838	5,299	3,018	1,816	1,141	736
Spain	3,992	1,914	1,035	599	358	218
UK	9,489	5,541	3,178	1,913	1,187	759
Sweden	1,615	1,100	738	502	350	246
EU5+	44,310	24,159	13,998	8,554	5,419	3,504

3.6.1 Intervention thresholds

Within the context of osteoporosis, an intervention threshold can be defined as the 10-year probability of osteoporotic fracture at which treatment becomes acceptable [15, 79–81]. When defining intervention thresholds it is necessary to both consider clinical and health economic factors. It is important that there is sufficient clinical evidence regarding the efficacy and safety of interventions in those patients deemed eligible for treatment at or above a given threshold. It is also important that the treatments are cost-effective interventions. The cost-effectiveness analysis has the advantage that it incorporates clinical, epidemiological and economic data.

Intervention thresholds were, until recently, largely determined on the basis of the T-score for BMD, and usually with little consideration of cost-effectiveness. Current guidance in several European countries reflects this legacy (see Chapter 2). The concept of developing intervention thresholds in osteoporosis based on cost-effectiveness began in Europe in the early 2000's at which time intervention thresholds were expressed as the hip fracture probability above which a given intervention became cost-effective [15, 79–81]. In a study by Borgström et al. [81] the 10-year risk of hip fracture at which intervention became cost-effective was estimated for 7 countries. As can be seen in Table 42 the intervention threshold increased with age and varied somewhat between countries. Reasons for the variation between countries include differences in fracture risk, willingness to pay (WTP) for a QALY and differences in drug price (alendronate in this example). The analysis was conducted before alendronate became available as a generic. Using current prices of generic alendronate would markedly decrease the fracture risk at which treatment would be appropriate from a cost-effectiveness perspective. This type of analysis was not incorporated into practice guidelines largely because there were no easily available clinical tools to assess hip fracture probability.

Table 42 Ten-year hip fracture probability (%) at which intervention becomes cost-effective [81]

Age	Australia	Germany	Japan	Spain	Sweden	UK	USA
50	1.93	1.48	1.14	3.05	1.38	1.02	1.09
55	3.41	2.65	2.17	5.32	2.59	2.03	2.07
60	5.64	3.65	3.11	8.73	3.55	3.18	2.76
65	6.04	4.80	3.94	10.83	4.58	4.35	3.95
70	8.73	6.88	5.61	14.66	6.56	5.70	6.61
75	10.82	8.83	6.95	18.04	8.25	7.43	7.97
80	13.11	10.52	8.05	18.91	9.33	8.44	9.27
85	11.57	9.49	7.74	17.49	8.35	7.46	9.15
90	10.76	8.19	7.30	15.79	7.39	6.48	8.87

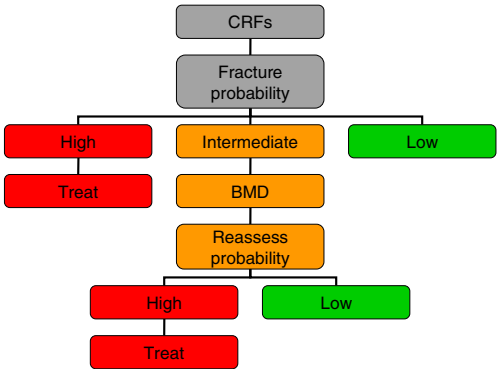
The advent of FRAX in 2008 provided clinical tools for the calculation of fracture probability which have been applied to the development of intervention thresholds [82]. Application of FRAX to clinical practice demands a consideration not only of the fracture probability at which to intervene, (an intervention threshold) but also for BMD testing (assessment thresholds). There have been two approaches to the development of guidelines based on fracture probability. The first is to 'translate' current practice in the light of FRAX and justify the thresholds developed by cost-effectiveness analysis, and the second has been to determine the threshold fracture probability at which intervention becomes cost-effective. The second approach has been used in North America [83, 84], whereas the former has been favoured in Europe.

The UK guidance for the identification of individuals at high fracture risk developed by NOGG is an example of the translation of former guidance provided by the Royal College of Physicians (RCP) [85, 86] into probability-based assessment [87]. As with the RCP guidance, the strategy is based on opportunistic case-finding where physicians are alerted to the possibility of increased fracture risk by the presence of CRFs. The CRFs used differ somewhat from those of the RCP, and comprised those used in the FRAX algorithms together with low BMI (<19 kg/m^2).

The RCP guidance indicates that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test, and the management of women over the age of 50 years on this basis has been shown to be cost-effective [23]. For this reason, the intervention threshold set by NOGG was at the fracture probability equivalent to women with a prior fragility fracture without knowledge of BMD [88]. The same intervention threshold was applied to men, since the effectiveness of intervention in men is broadly similar to that in women for equivalent risk [89].

In addition to an intervention threshold, assessment thresholds for the use of BMD testing were devised. The concept of assessment thresholds is illustrated in the management algorithm given in Fig. 23 [14]. The management process begins with the assessment of fracture probability and the categorisation of fracture risk on the basis of age, sex, BMI and the CRFs. On this information alone, some patients at high risk may be offered treatment without recourse to BMD testing. As noted, many guidelines recommend treatment in the absence of information on BMD in women with a previous fragility fracture. Many physicians would also perform a BMD test, but frequently this is for reasons other than to decide on intervention for example, as a baseline to monitor treatment. There will be other instances where the probability will be so low that a decision not to treat can be made without BMD. An example might be the well woman at menopause with no clinical risk factors. Thus not all individuals require a BMD test. The size of the intermediate category in Fig. 23 will vary in different countries, but a pragmatic strategy was used by NOGG because of the limited facilities for BMD testing in the UK [90].

Fig. 23 Management algorithm for the assessment of individuals at risk of fracture [14]

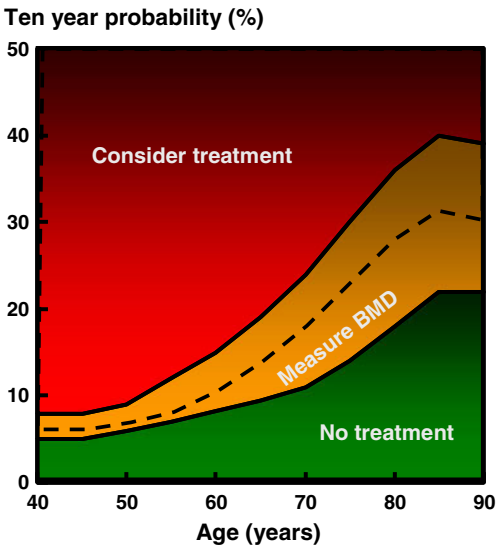


The NOGG management strategy requires consideration of two additional thresholds:

- a threshold probability below which neither treatment nor a BMD test should be considered (lower assessment threshold)
- a threshold probability above which treatment may be recommended irrespective of BMD (upper assessment threshold)

The lower assessment threshold was set to exclude a requirement for BMD testing in women of average BMI (24 kg/m^2) with weak or no clinical risk factors, as given in the RCP and European guidelines. The upper threshold was chosen to minimise the probability that a patient characterised to be at high risk on the basis of clinical risk factors alone would be reclassified to be at low risk with additional information on BMD [91]. The management algorithm is shown in Fig. 24 and summarised thereafter [87].

Fig. 24 NOGG management chart for osteoporosis showing the relationship between 10-year probability of a major fracture and age. The dotted line gives the intervention threshold [87]



This translational approach from existing treatment guidelines is characterised by an intervention threshold that increases progressively with age. The major reason for this is that the source guidelines took little or no account of age. In the UK, for example, intervention is recommended in women with a prior fragility fracture, irrespective of age. Since age is an important independent determinant of fracture risk, the fracture probability of an individual with a prior fracture is higher at the age of 70 years than at the age of 50 years. This age-dependent increase in the intervention threshold is not found when intervention thresholds are derived from health economic analyses alone [87].

The NOGG guideline provides an opportunity to apply the same approach to other countries and to determine the burden of disease in terms of FRAX. In other words to determine the number of individuals that have a fracture probability that is equivalent to or exceeds the age and country specific probability of fracture in a woman with a prior fragility fracture

The 10-year probability of a major osteoporotic fracture equivalent to women with a previous fracture (no other clinical risk factors, an average body mass index and without the knowledge of the patient's BMD) are provided in Table 43 for the EU5 countries and Sweden.

Table 43 FRAX 10-year probability (%) of a major osteoporotic fracture in women with a previous fracture (no other clinical risk factors, a body mass index of 24 kg/m^2 and without BMD)

Age	Germany	UK	Spain	France	Italy	Sweden
52	7.1	8.2	3.7	5.5	7.4	10.1
57	7.8	10.6	4.6	6.3	8.5	13.0
62	10.2	14.0	6.2	8.0	11.2	17.3
67	13.9	18.2	9.0	11.1	15.1	22.5
72	18.1	21.6	12.6	15.8	18.9	28.8
77	23.2	25.3	18.0	22.2	23.9	35.5
82	28.9	30.1	23.5	30.4	29.9	41.0
87	30.6	33.2	23.6	36.0	31.0	41.2

The proportion of men and women who exceed this threshold value was computed by simulation based on the distribution of the risk-score among the cohorts used by WHO to develop FRAX and the epidemiology of fracture and death in each EU5 country. Table 44 and Table 45 show the proportion of men and women in the EU5 with a probability of major osteoporotic fracture exceeding that of a woman with a previous fracture and no other CRFs, an average BMI, and unknown BMD.

The proportion of the population that could be eligible for treatment varied between countries and by age and sex. The relative difference between countries is larger in men

than in women. The UK appears to have one of the highest proportion of women falling above the threshold but lowest proportion of men. This variation across countries is caused by differences in fracture risk between women and men and differences in population prevalences of the risk factors used by FRAX.

Table 44 Proportion (%) of men at each age group that have a probability for osteoporotic fracture above that equivalent to women with a prior fracture and a BMI of 24 kg/m^2

Age group	France	Germany	Spain	Italy	UK	Sweden
50-55	2.5	3.4	3.1	0.7	0.9	2.6
55-60	4.5	6.8	6.3	1.7	1.0	2.2
60-65	2.6	3.8	3.4	2.1	1.2	1.9
65-70	1.9	2.1	2.1	2.3	1.5	2.1
70-75	2.2	2.2	2.2	2.5	1.5	3.1
75-80	2.5	2.6	2.3	3.2	1.4	3.6
80-85	2.4	3.0	2.6	4.1	1.2	2.8
85-	1.5	2.3	1.8	3.5	0.9	1.3
All (weighted)	2.7	3.6	3.3	2.2	1.2	1.3

Table 45 Proportion (%) of women at each age group that have a probability for osteoporotic fracture above that equivalent to women with a prior fracture and a BMI of 24 kg/m^2

Age group	France	Germany	Spain	Italy	UK	Sweden
50-55	19.1	16.2	20.5	22.4	19.5	16.4
55-60	17.6	15.0	16.3	21.4	20.7	19.0
60-65	19.7	17.9	19.4	20.0	20.7	20.4
65-70	23.2	21.7	23.1	21.8	21.2	23.2
70-75	23.0	21.6	22.7	21.6	21.5	22.9
75-80	22.9	21.0	22.6	21.2	21.1	22.9
80-85	20.8	19.1	20.3	18.7	19.9	20.4
85-	17.7	17.1	17.4	16.3	18.7	16.7
All (weighted)	20.2	18.6	20.2	20.7	20.5	20.1

The number of women and men that could be considered eligible for an osteoporosis treatment in EU5 based on the translational approach is shown in Fig. 25, 26 and Table 46. In all, 13.0 million women and 1.5 million men fall above the threshold probability for treatment. The rank order for women follows the same pattern as the total population sizes, i.e., Germany has the most patients and Sweden the least. Men however do not follow the same order. Germany has the most patients above the threshold and Sweden the least but UK stands out as having rather few patients above the threshold relative to its population size.

Fig. 25 Number (in thousands) of women at each age group that have a probability for osteoporotic fracture above that equivalent to women with a prior fracture and a BMI of 24 kg/m^2

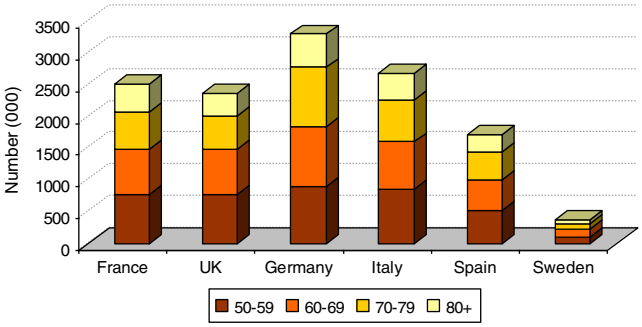


Fig. 26 Number (in thousands) of men at each age group that have a probability for osteoporotic fracture above that equivalent to women with a prior fracture and a BMI of 24 kg/m^2

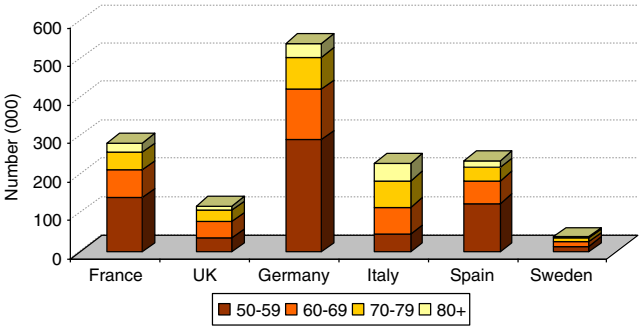


Table 46 Number (in thousands) of women and men at each age group that have a probability for osteoporotic fracture above that equivalent to women with a prior fracture and a BMI of 24 kg/m^2

	France	UK	Germany	Italy	Spain	Sweden	EU5+
Women							
50–54	409	392	495	454	309	47	2106
55–59	367	377	414	402	213	54	1828
60–64	394	400	410	386	238	63	1891
65–69	311	323	526	361	246	62	1829
70–74	300	281	556	359	220	46	1762
75–79	295	231	376	309	222	38	1472
80–84	232	176	278	221	153	29	1089
85+	207	185	247	195	122	29	985
Men							
50–54	51	18	106	14	46	8	243
55–59	89	18	185	31	80	6	409
60–64	49	22	85	38	39	6	239
65–69	23	21	47	34	20	6	151
70–74	24	17	49	34	18	6	147
75–79	23	12	35	34	17	5	126
80–84	16	7	25	29	13	3	93
85+	7	4	11	18	6	1	47

The translational approach is a fairly straightforward method to determine country-specific intervention thresholds using the FRAX algorithm. It acknowledges current treatment guidelines, but the intervention thresholds are not directly linked to, or estimated from, a cost-effectiveness analysis. However, it is still important to evaluate whether the thresholds for intervention using the translational approach provide a cost-effective treatment strategy. Relating the results from a recent study that estimated the cost-effectiveness of generic alendronate compared to no treatment using the FRAX tool for fracture risk estimation (further described in Chapter 2) treatment would be cost-effective at and above the threshold probability at any age in the UK [23]. Similar studies using FRAX directly as an instrument for fracture risk estimation within the cost-effectiveness analysis have not yet been conducted for alendronate in other countries.

Updated intervention thresholds based on cost-effectiveness using a generic price would likely suggest that people at very low fracture risks, generally not considered to be osteoporotic, would be eligible for treatment. These low-risk patients are difficult to identify in normal current practice and identification of such patients would require screening programs. However, the implementations of such a programme would be associated with additional costs for identification which would need to be considered in the cost-effectiveness analysis and the thresholds and to date, few such studies have been carried out. Another issue is that there is a lack of available clinical evidence on the fracture risk reduction with available drugs in low fracture risk populations. For these reasons intervention thresholds based on the translational approach were used in this report in Chapters 4 and 6 when analysing the treatment uptake and estimating the future burden of osteoporosis.

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4 Burden of osteoporosis

Summary

The objective of this section is to estimate the current burden of osteoporosis in the five largest countries in the European Union (Germany, France, the UK, Italy and Spain), as well as Sweden.

The key messages from this chapter are:

Cost of illness studies estimate the cost of a disease. They give no direct guidance of how resources should be allocated but may provide information concerning the level attention a disease should be awarded by health care policy makers.

A previously published cost of illness model, populated with the latest cost, utility, and epidemiological data, was used to estimate the burden of osteoporosis in terms of costs and QALYs in the EU5+.

The total health burden, measured in terms of lost QALYs, was estimated at approximately 850,000 QALYs for EU5+.

The annual number of QALYs lost ranged from about 250,000 in Germany to 39,000 in Sweden.
The total annual value of lost QALYs in the EU5+ was estimated at €47 billion.

The total cost burden, including pharmacological prevention, of osteoporosis in EU5+ was estimated at €30.7 billion (corresponding to approximately 3.5% of the total spending on health care in the analysed countries).

70% of the total costs were estimated to be incurred in individuals older than 74 years.
Hip fractures were estimated to account for 54% of the costs, other fractures 40%, vertebral fractures 5%, and wrist fractures only 1%.

A majority of the total costs burden could be attributed to incident fractures while pharmacological prevention and treatment management only represented 4.7% of total costs (ranging from 1.9% in Sweden to 14.7% in Spain).

The economic burden of osteoporotic fractures for the EU5 exceeds those for migraine, stroke, multiple sclerosis, and Parkinson's disease, and is similar to the burden of rheumatoid arthritis.

4.1 Introduction

Cost of illness studies estimate the cost of a disease. They give no direct guidance of how resources should be allocated but may provide information concerning the level of attention a disease should be awarded by health care policy makers. Cost of illness studies play an important role in the understanding of disease implications and may therefore aid decisions concerning societal resource allocation for research, development, and funding of new treatments. Results from cost of illness studies can also be utilised to assess the value of medical progress. Another important aspect is that cost of illness studies also provides information about who bears the burden of a disease.

The objective of this chapter is to estimate the current burden of osteoporosis in the five largest countries in the European Union (Germany, France, the UK, Italy and Spain) as well as Sweden. The burden of osteoporosis will also be compared to similar estimates for other diseases.

4.2 Methods and materials

A cost of illness study can take on a societal perspective (includes all cost carried directly or indirectly by society) or a payer perspective (usually includes all costs carried by the health care and social system). The present study included costs from a societal perspective and the burden of osteoporosis was measured in terms of fracture events, loss of QALYs, and in monetary terms including costs of fractures and treatment. A model previously used to estimate the burden of osteoporosis in Sweden [1] was adapted to the countries included in the present study. A literature search was performed to identify the best available utility, epidemiological, and economic data used to populate the model. The epidemiological data used in the analysis are described in Chapter 3.

The three most common sites of osteoporotic fracture (hip, vertebral and wrist) were included in the model as well as a combination of "other" osteoporotic fractures (i.e. pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and lower femur). Below the age of 50 years, the risk of osteoporotic fractures at a societal level is negligible, and data on for example costs and quality of life (QoL) are limited. Therefore, only fractures occurring in individuals 50 years of age or older and related consequences were included in the analysis.

4.2.1 Model design

The model employs a prevalence-based bottom-up approach [2] that contains the number of cases within a defined period of time multiplied by the corresponding disease-related consequences. Fractures often lead to increased costs and morbidity for several years after fracture. The consequences related to fracture can therefore be divided into an acute or incident phase and a long-term

(prevalent) phase. In the acute phase (in this report defined as the first year after fracture), the costs are higher and the health effects worse than in the following prevalent phase (defined as the period beyond the first year after fracture). Therefore, we captured the relevant fracture-related costs and health effects within a defined time period for both incident (i.e., fractures that occur within the year of analysis) and prevalent fractures (i.e., fractures that occurred in previous years but still have an impact on costs and quality of life during the study period). Further details regarding the calculation of the burden of fractures are described in Borgström et al. [1].

4.2.2 Fracture-related costs

First-year hip fracture-related direct costs were available for all countries except France and Spain. The French and Spanish hip fracture costs were therefore derived from UK data [3] by adjusting for differences between the countries in price levels. In those cases where the direct costs related to vertebral fracture and wrist fracture were missing, the cost was derived via morbidity equivalents as estimated by Kanis et al. [4]. Morbidity equivalents can roughly be described as the morbidity a fracture type confers compared to that of a hip fracture, and costs were assumed to follow the same pattern. This assumption has been shown to be appropriate, at least in a US setting [5].

Fracture-related productivity losses, only applicable to individuals less than 65 years of age, have been estimated to be small [6] and were only taken into account if they were already included in the cost estimates found in the literature.

To calculate the cost of "other" fractures for Sweden it was assumed that femoral and pelvic fractures were equivalent to hip fractures; humerus fractures were assumed to be equivalent to vertebral fractures; and fractures of the rib, clavicle, scapula and sternum were assumed to be equivalent to forearm fractures. The costs were then age-weighted to represent the age distribution of these fractures [4]. For the other countries, the cost of "other" fractures was calculated as a share of the first-year hip fracture related direct costs by assuming the same ratio of first-year hip fracture related direct costs and "other" fracture cost as in Sweden.

All costs are given in Euros (€) and in 2010 year's prices. The consumer price index was used to inflate costs when needed [7]. The first-year fracture costs for the six countries are shown in Table 47. Where age-differentiated costs were available these were used (presented in ranges in Table 47) otherwise a single estimate was used for all ages.

Table 47 First year direct costs of a hip, vertebral, forearm and other fracture (€, 2010). Age-differentiated costs are presented in ranges.

	Hip	Clinical vertebral	Forearm	Other
France	12,030-19,004 [3, 8][b]	2,999 [3][b]	1,374 [3][b]	3,870-12,059 [c]
Germany	19,218 [9]	5,585-6, 845 [9]	1,173 [9][a]	6,182-13,130 [c]
Italy	19,602 [10]	4,336 [10][a]	1,197 [10][a]	6,306-13,393[c]
Spain	9,421-17,350 [3, 8][b]	2,349 [3][b]	1,076 [3][b]	3,030-9,444[c]
Sweden	12,870-19, 667 [6]	2,048-14, 219 [6]	2,401 [6]	4,140-9,096
UK	11,055-20,359 [3, 8]	2,756 [3]	1,263[3]	3,556-11,081 [c]

[a]Estimated as a fraction of hip fracture cost based on the morbidity equivalents in Kanis et al. [4].

[b]Imputed from the UK data by adjusting for differences in health care price levels.

[c]Imputed from Swedish estimate [4, 6].

There are currently no published studies that provide robust estimates of the long-term fracture costs based on empirical patient samples. Therefore, hip fracture costs in the second and following years are usually based on the proportion of patients that become institutionalised for the long-term after fracture [11, 12]. The proportion of patients that has transitioned from independent living to long-term care one year after hip fracture increases with age (approximately 6% at age 50 to 23% of patients older than 90 years). Patients who at the time of fracture already reside in long-term care were assumed to not have any additional long-term fracture related costs and the rates were adjusted accordingly. Moreover, the proportion that is admitted to long-term one year after fracture must be down-adjusted to account for the risk of being admitted to long-term care due to causes not related to the hip fracture itself. The annual risk of being institutionalized in long-term care in the general population in Sweden is approximately 0.1%, 0.5%, and 2% for a 65-, 75- and 85-year old individuals, respectively [13]. Data on the proportion of patients that transition to nursing home after a hip fracture and on the incidence of transition to nursing home in the general population are scarce in the published literature and Swedish data were therefore used for all countries. This is a reasonable

proxy for countries in Northern Europe but may be an overestimation for countries in Southern Europe, where long-term care to a larger extent is provided by informal care givers (e.g., a spouse or child). Informal care is however also associated with societal costs like productivity losses, lost leisure time, and out-of-pocket expenses. The true net effect is unknown.

By multiplying the adjusted proportions with the yearly cost of a nursing home cost (Table 48), the annual hip fracture cost beyond the first year after a fracture could be obtained. Wrist fracture and vertebral fracture were assumed to not incur any costs beyond the first year after fracture.

Table 48 Yearly cost at long-term care facility (€, 2010)

Country	Long-term care cost	Reference
France	31,512	[8] [a]
Germany	34,534	[14] [b]
Italy	50,202	[10]
Spain	51,786	[15]
Sweden	57,247	[6]
UK	33,756	[8]

[a]Imputed from the UK long-term care cost adjusting for differences in the health care price levels

[b]An average of 4 long-term care facilities

4.2.3 Quality of life loss related to fractures

Loss of QoL can be a result of fracture consequences in several health domains, such as pain with loss of physical functioning as well as social and mental consequences. The physical functioning includes loss in mobility and self-care. The impact on activities and role are important social impairments whilst mental health is affected by depression, anxiety and low self-esteem [16]. The health burden of osteoporosis can be measured by disutility or loss in utility resulting from the disease, as well as increased mortality. Utilities reflect the QoL, normally ranging between zero (reflecting death) and one (reflecting full health).

The utility loss from an osteoporotic fracture varies depending on the site of fracture. Hip and vertebral fractures result in substantial disutility whereas forearm fractures are associated with some decrements in utility but considerably less and for a shorter period of time. The loss of utility is greatest for all fractures in the first year and decreases in subsequent years. On average, patients with forearm fractures regain their pre-fracture utility after 12 months [17].

The utility the first year after hip, vertebral and wrist fracture relative to the age-specific utility in the normal population (i.e. utility multiplier) has been estimated to be 0.7, 0.59 and 0.956 respectively [18]. The QoL lost from fracture does not differ significantly between women and men and the relative loss has shown to be of the same magnitude irrespective of whether the patient had had a prior fracture or not [6]. Quality of life in the subsequent years after a hip fracture was assumed to be 80% of that of a healthy individual [18]. Based on the findings that radiographically defined vertebral fractures reduce QoL by approximately 9% when the fracture had occurred at a unknown time [19], it was conservatively assumed that the quality of life loss related to clinical vertebral fractures in the second and following years was 0.05 which gave a multiplier of 0.929 [20]. There are no studies suggesting that wrist fracture is associated with a long-term reduction in QoL and it was therefore assumed that wrist fracture did not have an impact on QoL beyond the first year after fracture. No significant difference in QoL has been established for patients who were hospitalised and those who were not [17].

Quality of life estimates for the general population measured with EQ-5D were only available for Sweden and the UK and the other countries were therefore assumed to value their QoL similarly to the population of UK. Age-specific utilities after fracture are derived by multiplying the utility multipliers, described above, with the QoL values of the general population. For example a 75 year old man (average utility of the general population at age 72 years = 0.72) who sustains a hip fracture has a disutility of 0.216 (=0.72*(1–0.7)) in the year after fracture.

4.3 Results

4.3.1 QALYs lost due to fractures

The data presented in Chapter 3 on fractures and mortality were combined with the QoL data above to estimate the annual number of lost QALYs due to fractures. For the estimation of QALYs lost due to fracture related deaths it was assumed that individuals who die from a fracture will do so on average four months after the fracture [1]. The burden of fractures, in terms of lost QALYs, was estimated at 845,401 QALYs in the EU5 and Sweden (Fig. 27, Fig. 28 and Table 49) and 806,745 QALYs when considering the EU5 alone. Among the EU5, Germany was estimated to have highest number of lost QALYs which is a result of high fracture incidence and prevalence, and a large population. Sweden incurs the smallest total QALY loss. The annual number of QALYs lost ranged from about 250,000 in Germany to 39,000 in Sweden.

Fig. 27 Estimated number of QALYs lost due to fractures in women during 2010

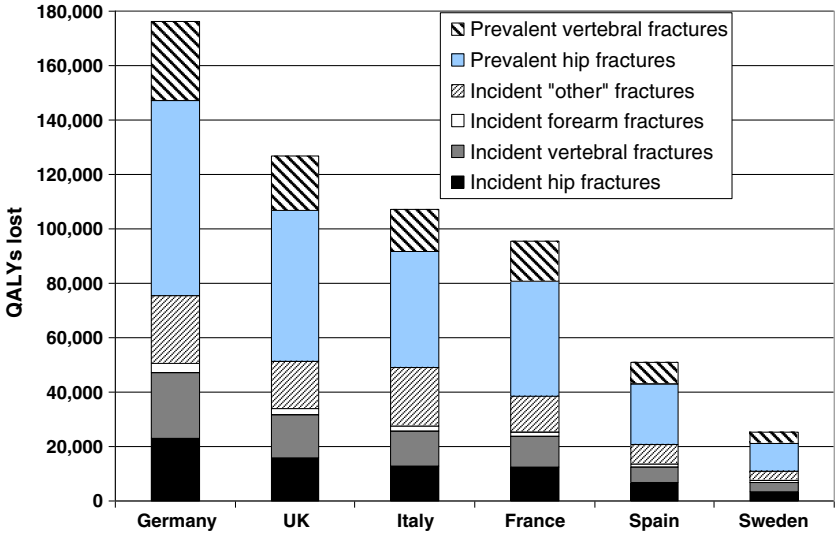
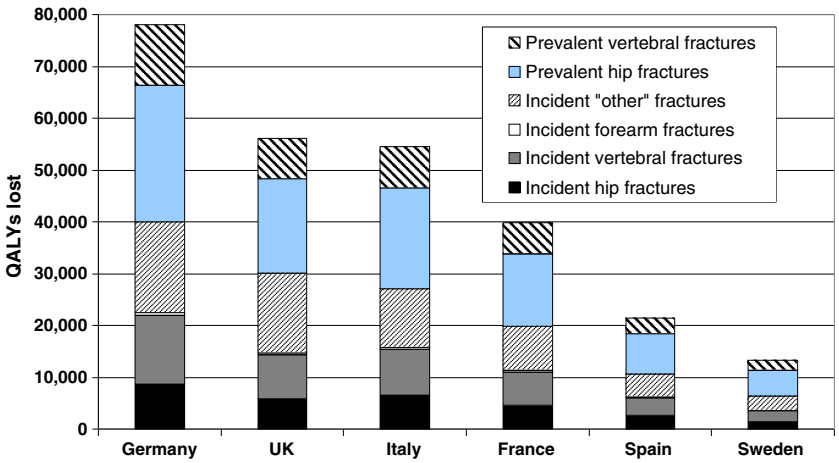


Fig. 28 Estimated number of QALYs lost due to fractures in men during 2010



A large component of the QALYs lost arises in the subsequent years after fracture as a consequence of the long-term disability from osteoporotic fractures. This pattern is less pronounced in men, because of higher absolute mortality after fracture in men than in women. Fracture related mortality (see Chapter 3) during the first year after incident hip, vertebral, and "other" fractures represented approximately 1% and 3% of the total QALY-loss in women and men, respectively.

Even though common, wrist fractures only represented a marginal share of the estimated fracture related disability. The negligible impact of forearm fracture on QALY-loss in the total population is due to its relatively small impact on QoL during the first year after fracture, and the complete long-term recuperation after fracture.

Table 49 Estimated number of QALYs lost due to fractures during 2010

	Women						
	Germany	Italy	UK	France	Spain	Sweden	EU5+
Incident hip fractures	22,861	16,006	13,017	12,498	6,754	3,517	74,654
Incident vertebral fractures	24,254	15,839	12,732	11,361	5,859	3,398	73,443
Incident forearm fractures	3,374	2,206	1,822	1,584	823	463	10,274
Incident "other" fractures	24,987	17,186	21,664	13,228	7,212	3,719	87,995
Prevalent hip fractures	71,603	55,500	42,502	41,936	22,404	10,150	244,097
Prevalent vertebral fractures	29,274	20,202	15,363	14,813	7,909	4,057	91,618
Total	176,354	126,939	107,102	95,420	50,962	25,303	582,080
	Men						
	Germany	UK	Italy	France	Spain	Sweden	EU5+
Incident hip fractures	8,736	5,787	6,570	4,638	2,586	1,457	29,773
Incident vertebral fractures	13,127	8,500	8,856	6,417	3,419	2,053	42,373
Incident forearm fractures	675	427	387	307	153	100	2,049
Incident "other" fractures	17,408	15,309	11,310	8,493	4,477	2,686	59,683
Prevalent hip fractures	26,461	18,307	19,422	13,908	7,744	5,000	90,842
Prevalent vertebral fractures	11,707	7,724	8,002	6,038	3,073	2,056	38,600
Total	78,114	56,055	54,547	39,802	21,452	13,352	263,321

4.3.2 Value of lost QALYs

There is no international standard on the societal value of a QALY lost and official numbers for the value of a QALY are rarely stated. In the UK, the WTP lies within the range of GBP 20,000–30,000 (about €23,000–34,000 at current exchange rates) per QALY. Rather than quantifying the value of QALYs lost in a burden of illness estimation, such as this one, this value is generally used for evaluating the cost-effectiveness of healthcare interventions. The high end of the range can be acceptable if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure [21]. 600,000 SEK (approximately €54,000) is a commonly used as the value/QALY for Sweden and is based on the value of statistical life (i.e. a measure that summarizes tradeoffs between monetary wealth and fatal safety risks) estimated by the Swedish National Road Administration [22, 23].

For the purpose of this study the value of a QALY was related to the economic performance of the included countries, as a proxy for a country's ability to pay for health care (Fig. 29). WHO has suggested a value of a QALY of 3 times the GDP per capita, but this multiplier was suggested for developing economies. Borgström et al. [24] have suggested a WTP of 2 xGDP/capita for industrialised countries, which is more appropriate for the countries included in this report. Assigning a value of 2 xGDP/capita per QALY to the QALYs lost (Fig. 29) resulted in estimates of €14.9 billion, €9.2 billion, €8.6 billion, €8.2 billion, €3.4 billion, and €2.7 billion for lost QALYs in Germany, Italy, UK, France, Spain, and Sweden, respectively (Fig. 30). The total annual value was thus estimated at €44.3 billion in the EU5 and at €47 billion when Sweden was included. It should be noted that this number does not represent an avoidable monetary cost, but rather the annual societal value of QoL and length of life attributable to fragility fractures.

Fig. 29 Willingness to pay per QALY based on GDP/capita in EU5 and Sweden

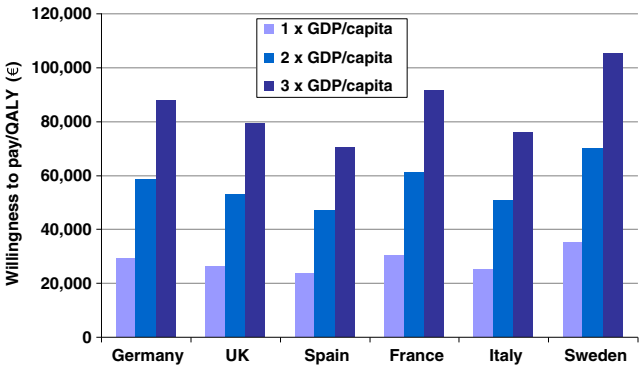
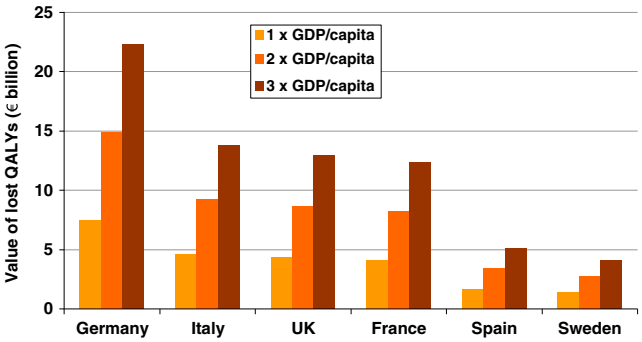


Fig. 30 Value of lost QALYs in EU5 and Sweden



4.3.3 Economic burden of osteoporosis

The economic fracture burden in a country depends on a variety of factors, including the age specific fracture risks, the population's size (Table 50), age and sex distribution, the cost per fracture, the cost of residing in a nursing home, and the proportion of hip fracture patients requiring nursing home care after fracture.

Table 50 Burden of fractures in relation to population and health care spending

Country	Population (000)	Health care spending (000 €)	% of health care spending on fractures	Burden per capita (€)
Sweden	9,294	31,000	4.6%	153
Spain	45,000	95,000	3.0%	64
France	62,634	214,000	2.2%	76
UK	61,899	142,000	3.9%	89
Italy	60,098	138,000	5.1%	117
Germany	82,056	252,000	4.6%	111
EU5	311,687	841,000	3.7%	94
EU5+	320,981	871,000	3.5%	96

The total monetary osteoporosis burden 2010 in the EU5 (including pharmacological intervention) was estimated at €29.3 billion, or €30.7 billion when Sweden is included (Table 51). A majority of costs could be attributed to incident fractures whilst pharmacological intervention and administration of the treatment only represented 4.7% of total costs (Table 52). The share ranged from 1.9% in Sweden up to 14.7% in Spain. The annual expenditure of €30.7 billion corresponds to approximately 3.5% (Table 50) of the total spent on health care in the analysed countries (2.2% in France to 5.1% in Italy). It should be noted, however, that not all fracture-related costs come from the countries' healthcare budgets (e.g., long-term care, informal care, community care).

The estimated burden per capita (total population) appeared to correlate reasonably with fracture risk, as estimated by FRAX (Fig. 31). The risk population in Fig. 31 was arbitrarily chosen but still provides a good illustration of how age-specific fracture risk is a driver of costs. The highest direct cost per capita was estimated in Sweden (€153/capita) and the lowest in Spain (€64/capita) (Table 50).

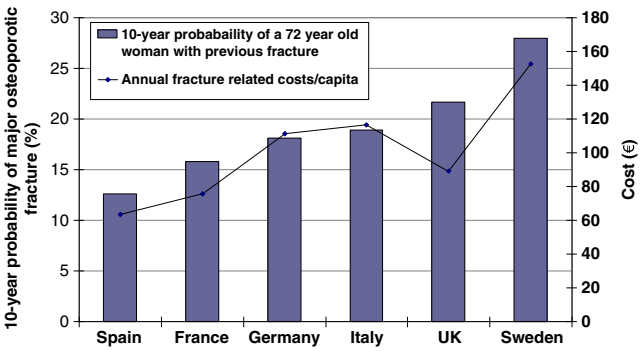
Table 51 Monetary burden of fractures 2010 in EU5 and Sweden (million €)

Country	Cost of incident fractures	Cost of prevalent fractures	Treatment + administration of treatment	Total
Sweden	863	528	27	1,418
Spain	1,401	1,043	420	2,864
France	3,266	1,152	327	4,744
UK	4,078	1,315	121	5,515
Italy	4,275	2,386	348	7,010
Germany	6,854	2,057	235	9,146
EU5+	20,736	8,482	1,479	30,696

Table 52 Shares of total cost burden by cost type

Country	Cost of incident fractures	Cost of prevalent fractures	Treatment + administration of treatment
Sweden	60.8%	37.2%	1.9%
Spain	48.9%	36.4%	14.7%
France	68.8%	24.3%	6.9%
UK	73.9%	23.8%	2.2%
Italy	61.0%	34.0%	5.0%
Germany	74.9%	22.5%	2.6%
EU5+	67.6%	27.6%	4.8%

Fig. 31 Cost of osteoporosis/capita and international variations in fracture risk



The monetary burden depends on a number of factors, of which the most important is that fracture risk and cost per fracture increase with age. The more costly hip fractures represent a larger share of all fractures in older individuals which is reflected in the distribution of the total cost burden over age groups (Fig. 32). Approximately 70% of the total costs were estimated to be incurred in individuals older than 74 years. Fractures sustained in women were estimated to account for 69% of the total cost (Fig. 33). Hip fractures were estimated to account for 54% of the costs, other fractures 40%, vertebral fractures 5%, and wrist fractures 2% (Table 53).

The estimate of 40% for "other" fractures may be perceived as a high figure given that most health economic evaluations of fracture prevention mainly focus on hip and vertebral fractures [23, 25–27]. However, such studies usually evaluate treatment in elderly osteoporotic women where the risks of hip and vertebral fractures are more elevated than that of the risk of "other" fractures. By contrast, the current study captured all fractures in all age groups.

The cost of clinical vertebral fractures is likely to be underestimated due to the difficulties of studying them. 9-33% of clinical vertebral fractures become hospitalised (depending on age [28]). Non-hospitalised fractures are seldom available in registers and are more difficult to include in observational studies [6]. Further, the cost estimation is complicated by the fact that many vertebral fractures do not come to clinical attention at all. Although the consequences after clinical vertebral fractures are likely worse than after morphometric subclinical vertebral fractures, it cannot be ruled out that the latter may also be associated with costs and morbidity.

Fig. 32 Total cost burden stratified by age

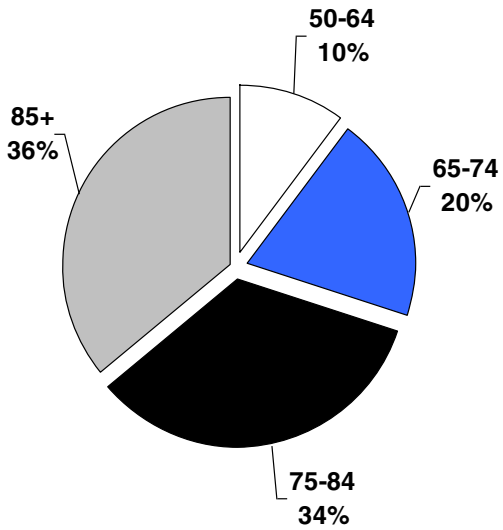


Fig. 33 Total cost burden stratified by sex

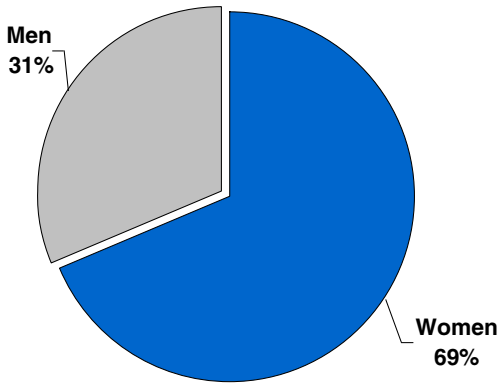


Table 53 Shares of total cost burden by fracture site

	Fracture site				
Country	Hip	Spine	Forearm	Other	All
Sweden	56.5%	10.3%	2.8%	30.3%	100%
UK	48.0%	3.1%	1.6%	47.3%	100%
France	56.3%	3.5%	1.8%	38.5%	100%
Germany	49.9%	7.6%	1.6%	41.0%	100%
Italy	56.8%	3.9%	1.4%	37.9%	100%
Spain	65.9%	2.6%	1.3%	30.2%	100%
EU5+	53.7%	5.0%	1.6%	39.7%	100%

The burden of fractures, expressed as the sum of the total cost and the value of QALYs, was estimated at €73.6 billion in the EU5 and €77.7 billion in EU5 and Sweden (Table 54). Germany was estimated to have the highest burden of €24 billion and Sweden the lowest burden of €4.1 billion.

The economic burden of fractures in the whole of Europe has previously been estimated at €36 billion in 2000 [29]. The estimate would, translated to 2010, be higher due to increased number of fracture, which is partly due to an aging population. Given that the economic burden of fractures in the current report also included the cost of prevalent fractures and cost of treatment, and that ten years have passed between these two studies, the estimate of €30.7 billion in EU5 and Sweden is reasonable.

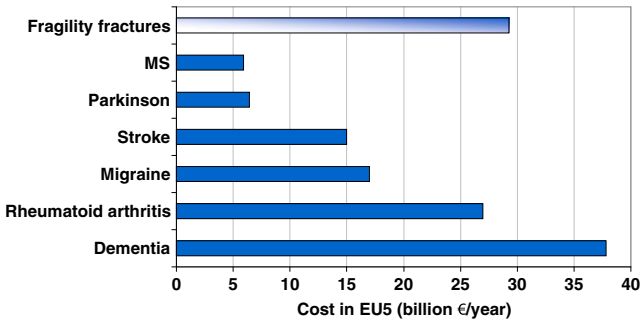
Table 54 The total cost of fractures and the value of QALYs in 2010 (billion €)

Country	Cost of fractures	Value of QALYs lost	Total burden
Germany	9.1	14.9	24.0
Italy	7.0	9.2	16.2
UK	5.5	8.6	14.1
France	4.7	8.2	13.0
Spain	2.9	3.4	6.3
Sweden	1.4	2.7	4.1
EU5	29.2	44.3	73.6
EU5+	30.7	47.0	77.7

4.3.4 Economic burden of osteoporosis compared to other diseases

The estimated total annual costs of osteoporosis may be compared to the cost of other diseases. The burden of various brain disorders in the EU5 in 2004 has been estimated at €38, €17, €5.9, €6.4 and €15 billion for dementia, migraine, multiple sclerosis (MS), Parkinson disease and stroke, respectively [30]. The total societal economic consequence of cardiovascular diseases in the EU5 in 2003 was estimated at €133 billion [31]. A report on the burden of rheumatoid arthritis estimated the total cost in the EU5 to €27 billion [32]. Thus also in relation to other common non-communicable diseases osteoporosis has major economic consequences for society. Fig. 34 illustrate that the economic consequences of osteoporotic fracture for the EU5 exceeds those for migraine, stroke, MS, and Parkinson's disease. The financial burden of rheumatoid arthritis is similar to that of osteoporosis.

Fig. 34 Cost of disease in EU5



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5 Uptake of osteoporosis treatments

Summary

This chapter provides a description of current uptake of osteoporosis treatments. In the absence of readily available information on the number of patients treated in most countries in Europe, we use international sales data on volume (mg) and price (€) from IMS Health, combined with estimations on how many should be eligible for treatment using a fracture risk threshold level. The analysis is based on France, Germany, Italy, Spain, Sweden and the UK.

The drugs included in the analysis are alendronate, etidronate, ibandronate, risedronate, zoledronic acid, raloxifene, strontium ranelate, teriparatide and PTH (1–84). Three out of the nine drugs received marketing authorization during the 1990s. The last drug to be marketed was PTH(1–84) in 2006.

The results are presented as sales (€ 2008) and defined daily dosages (DDDs) per 100,000 in population above 50 years of age. Also the number of patients on treatment during a year related to the number of patients that could be considered eligible for treatment was assessed.

Based on the analysis we conclude

Alendronate is the most commonly prescribed agent accounting for about 30% of the total sale value in the EU5. In volume, alendronate accounts for about 50% of the market. The uptake of osteoporotic treatments varies between countries (e.g., 11% of the population above 50 years in Spain compared with 3% in Germany).

The data do not indicate any clear correlation between the price of drug and the total volume of drug sold.

The treatment uptake of osteoporosis drugs has increased considerably, albeit from very low levels, since 1998.

There is a large gap between the numbers of women that are treated compared to the proportion of the population that could be considered eligible for treatment based on fracture risk.

Swedish prescription data showed a 20% lower uptake of alendronate compared with the sales data. This difference cannot be explained by parallel export and hospital based prescriptions and requires further investigation.

5.1 Introduction

Treatment uptake includes the analysis of the rate of uptake of a new drug to the market, and how many patients of those eligible for treatment are actually treated (i.e. have real access to the medication). In order to analyse the uptake of treatments in different countries data on the number of patients currently treated and the number of patients that should be treated in each country are required. Unfortunately, in most countries, individual patient data are not readily available and there are only a few European nations (e.g., the Nordic countries and Netherlands) that hold sufficiently large databases which could facilitate a detailed analysis on prescription use at an individual level. In the absence of country- and patient-specific data, we utilised international sales data in order to assess treatment uptake between countries and over time.

In this chapter we use international sales data between 1998–2008 on volume (mg) and price (€) from IMS Health to estimate the uptake of osteoporosis treatments in France, Germany, Italy, Spain, Sweden and the UK.

5.2 Methods and Data

IMS Health data are currently the only source of comparative data on sales of pharmaceuticals at an international level, but have a number of shortcomings which must be considered. In any country, it is unlikely that 100% of sales are captured, but it is difficult to define the magnitude of the underestimate. For some countries, it is known that part or all of hospital sales are omitted and that certain wholesalers or other channels of distribution are not included. Similarly, it is possible that sales are overestimated in some countries as a consequence of the sample of pharmacies and hospitals that provide data. Since IMS Health attempts to correct for under- and over-estimation, and in the absence of any additional information, we have refrained from an overall adjustment of the available sales figures.

Another difficulty may arise from parallel trade. Although drugs launched in the last two decades have generally a rather narrow price band across Europe, price control mechanisms, adaptation to distribution channels and currency fluctuations have created a price difference that give incentives for parallel trade. IMS Health adjusts the data for parallel trade but it is difficult to estimate the accuracy of these corrections. However, in a previous EFPIA report on rheumatoid arthritis [1] we have approached the issue by verifying data from Norway where parallel export was known to exist. Data from Farmastat (the organisation that collects sales from wholesalers who are legally obliged to exclude parallel export) were found to be very

similar to those reported by IMS Health. In this report we also performed a test of validity by comparing IMS Health data with actual data from the Swedish Prescribed Drug Register. The result from this analysis is presented in the results section.

An important component in the analysis of treatment uptake is how many patients are treated and IMS Health sales data allow for the estimation of how many treatment years the sales volume can cover. However, not all patients adhere perfectly to therapy, and such an approach would consequently result in an underestimation of the actual number of patients that have started a treatment since some patients only are treated for a part of the year. To correct for suboptimal adherence we estimated an adjustment factor from data from the Swedish Prescribed Drug Register. The adjustment factor was employed irrespective of country because similar data were not readily available for any other country. The following steps were included in the estimation of the number of individuals treated based on IMS Health sales data:

- The Defined Daily Dosages (DDDs) per 100,000 was estimated by dividing the mg per 100,000 patients by the DDD in mg for each drug. The DDD for each drug was derived from the WHO Anatomical Therapeutic Classification (ATC)/DDD database (http://www.whocc.no/atc_ddd_index/).
- The proportion of the total population in each country (all ages) that could theoretically be covered by a full year of treatment based on the sales volume can be estimated by dividing the DDDs per 100,000 in the population by 365 (days in a year). In this report this estimate is termed the population coverage.
- Almost all osteoporosis drugs are prescribed to patients 50 years or older (97.2% based on Swedish prescription data). Therefore, it was assumed that only patients 50 years or older were given osteoporosis treatments. The population coverage was thus adjusted to only reflect the part of the population at or above 50 years of age in each country.
- Based on an analysis of filled prescriptions from the Swedish Prescribed Drug Register between 2006 and 2009, it was estimated that the total volume of the prescription could cover 73% of the total observed time (i.e., the sum of the days from treatment start to end of the year) for all patients that were prescribed an osteoporosis treatment during this period. This estimate was not found to vary with age. This factor was used to approximate the number of patients being treated during a year for all countries.
- Additionally, to differentiate the uptake between men and women we assumed that 87% of the sales were directed to women and 13% to men (based on Swedish prescription data).

In a treatment uptake analysis, the number of individuals treated also needs to be related to the number of patients in the population that could be considered eligible for an osteoporosis treatment. However, this is not straightforward both due to different levels of fracture risks and guidelines between countries. In our analysis we used the translational approach (described in Chapter 3) assuming that the threshold level to be eligible to start treatment is the estimated country-specific fracture risk equivalent to a woman with a prevalent fracture and average weight at different ages based on the FRAX algorithm.

5.2.2 Treatments

5.2.2.1 Use

Table 55 shows the year of introduction in Europe (EMA marketing authorisation) for the available agents indicated for osteoporosis treatment. Out of the nine agents, three received marketing authorisation during the 1990s. The last product to be marketed was PTH (1–84) in 2006. Upon expiration of the patent of alendronate, generic versions of the medication started to become available in Europe in 2006.

Table 55 Year of first introduction in Europe

	Year
Bisphosphonates	
Alendronate	1995
Etidronate	1980
Ibandronate	2005
Risedronate	2000
Zoledronic acid	2005
SERMs	
Raloxifene	1998
Parathyroid hormones	
Teriparatide	2003
PTH (1–84)	2006
Strontium ranelate	2004

5.2.2.2 Price

The current annual drug prices in the EU5 and Sweden are shown in Table 56. There are variations in price between countries. UK has consistently the lowest price for all drugs. Although France, Germany, Italy and Spain have fairly similar price patterns, there are some notable differences such as the

high price of etidronate in Germany and low price of risedronate in Spain. In addition, the prices of alendronate vary, with particularly low prices in Sweden and UK compared with the other countries.

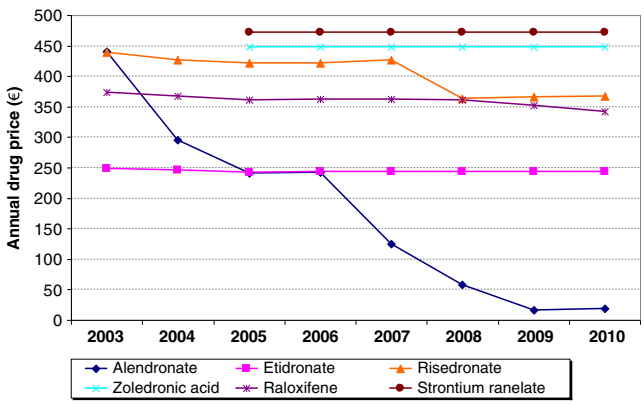
Table 56 Annual drug costs (pharmacy price €) in 2010 by country

	France[c]	Germany[d]	Italy[e]	Spain[f]	UK[b]	Sweden[a]
Alendronate	209	245	294	201	18	27
Risedronate	380	509	474	299	217	366
Etidronate	99	475	97	44	79	241
Ibandronate	327	576	524	416	188	NA
Zoledronic acid	410	562	529	417	242	443
Raloxifene	365	540	452	449	221	358
Strontium ranelate	579	611	665	644	285	468
Parathyroid hormone	NA	7,853	6,528	5,168	2,897	4,585
Teriparatide	4,829	7,700	7,445	5,220	3,024	5,174

Sources:
[a] www.fass.se
[b] British National Formulary
[c] www.vidalpro.net
[d] www.rote-liste.de
[e] www.agenziafarmaco.it
[f] www.portalfarma.com

Historical prices of drugs are difficult to extract in many countries. Fig. 35 shows the development of annual drug prices between 2003 and 2010 based on past decisions by Swedish Pharmaceutical Benefits Board (www.tlv.se). The prices for etidronate, strontium ranelate, raloxifene and zoledronic acid have all remained stable. Risedronate had a reduction in the price in 2008. The price of alendronate decreased markedly from 2003. It is notable that the price of alendronate was reduced before the introduction of generic substitutes. Prices for PTH (1–84) and teriparatide (not shown in the figure) remained stable since their introduction.

Fig. 35 Annual drug prices in Sweden between 2003 and 2010



5.3 Results

5.3.1 Market share and price analysis

The estimated market shares, based on value (€) and sales (DDDs), 1998 through 2008 in the EU5 are shown in Fig. 36 and Fig. 37. The value of the sales increased fairly rapidly until 2005 where the increase slowed down markedly. The slowdown in sales was mainly driven by the introduction of generic alendronate. The increase in sales in recent years is mainly related to the introduction of new drugs (ibandronate, strontium ranelate, zoledronic acid, PTH (1–84), and teriparatide). The increase in volume has almost been linear from 1998. The volume of sold alendronate has steadily increased whereas it has slightly decreased for risedronate and raloxifene in recent years.

In Table 57, the sales per product in 2008 and market shares based on total sales value and volume (DDDs) are shown. The large difference in market share for alendronate between sales and DDD is a reflection of the low price of the generic version of the drug. The same applies for teriparatide and PTH (1–84) but in the opposite direction. Due to comparatively high prices their market share in terms of price is much higher than the volume market share.

The total sales and DDDs per 100,000 of the population (all ages) per country are presented in Fig. 38. There is a marked difference between countries in the relation of sales and DDDs. This can be explained by differences in the market penetration and price of generic alendronate. In countries such as the UK and Sweden the price of generic alendronate is at very low levels compared to other countries. In Germany, Italy, France and Spain the price difference between generic versus branded alendronate is less, resulting in a lower market share of the generic version (Fig. 39). Another factor contributing to differences is that the perception of the performance of generic alendronate among physicians differs between countries.

Fig. 36 Estimated market shares in EU5 (sales in €, per 100,000 in whole population)

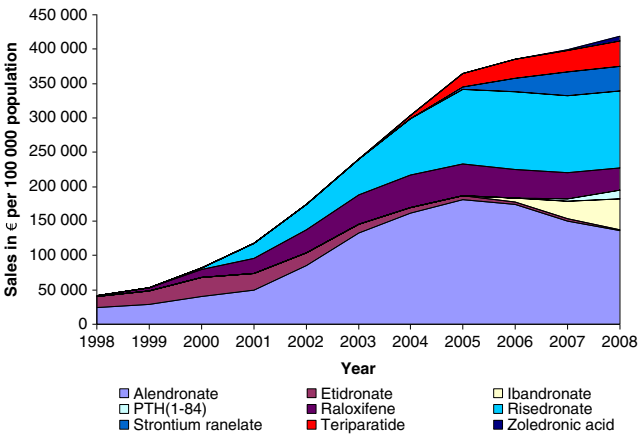


Fig. 37 Estimated market shares in EU5 (DDD per 100,000 in whole population)

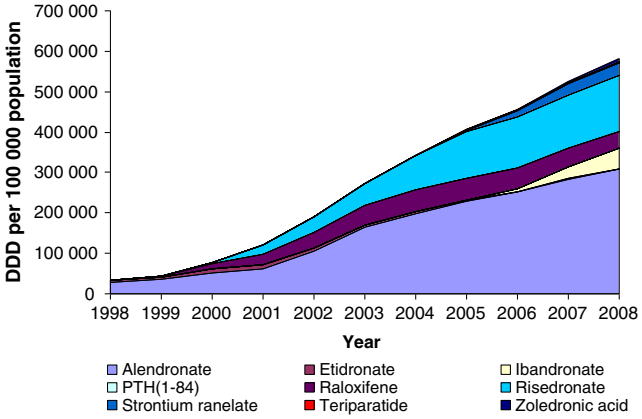


Table 57 Estimated sales in EU5 (ex factory prices) and market shares in 2008 based on IMS Health data

	Estimated Sales 2008(€, millions)	Estimated Market Share 2008 (price)	Estimated Market Share 2008 (DDDs)
Alendronate	416	32.4%	52.9%
Etidronate	6	0.4%	0.2%
Ibandronate	138	10.7%	8.8%
Risedronate	340	26.5%	23.9%
Zoledronic acid	21	1.6%	1.4%
Raloxifene	101	7.8%	7.1%
Strontium ranelate	110	8.6%	5.0%
Teriparatide	114	8.9%	0.7%
PTH(1–84)	37	2.9%	0.0%
Total	1,283	100%	100%

As can be seen in Fig. 4, the uptake of treatments for osteoporosis varies in the EU5+. The lowest uptake in terms of daily doses is seen in Sweden – country with high fracture rates. Conversely, the highest uptake is seen in Spain – a country with low fracture rates. The variations in drug uptake cannot however explain the heterogeneity of fracture rates [2]. The UK is ranked fourth in uptake, but sixth in expenditure due to the very low cost of generic alendronate.

Fig. 38 Estimated sales (€ 2008) and DDDs per country (per 100,000 population)

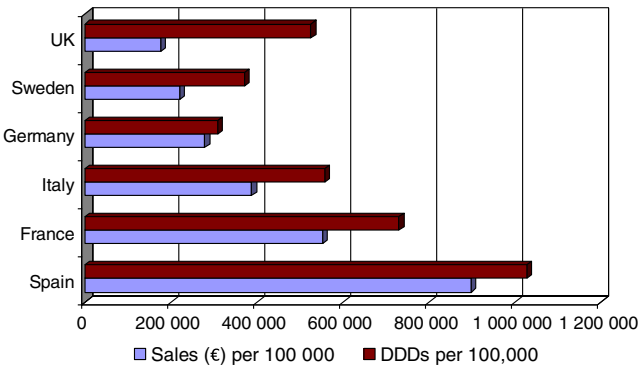
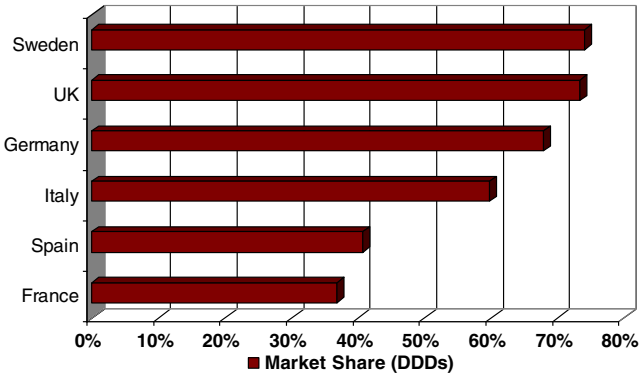


Fig. 39 Estimated market shares (DDDs) of alendronate in 2008



In the value of sales analysis (Fig. 40) it is apparent that the introduction of generic alendronate has impacted the value of sales differently. In Germany, Sweden and UK there is a clear break and reduction in the total sales from year 2006, which is not evident for the other countries. This is also observed when analysing the change in cost per DDD over time (based on prices from manufacturers) in Fig. 41. The price per DDD has been fairly consistent over all years in France, Italy and Spain, whereas in the UK and Germany it has decreased by 79% and 52%, respectively. In France, branded alendronate is prescribed in a formulation containing vitamin D which has not been challenged by a generic form. In addition, risedronate performs very well. These two parameters may explain the somewhat weaker effect of generic alendronate in France, together with the resistance of GPs to prescribe generics.

A factor that contributes to the reduction in sales value in the UK is the depreciation of the British Pound versus the Euro in recent years (about 13% depreciation between 2006 and 2008).

Fig. 40 Estimated annual sales (€) (per 100,000 population)

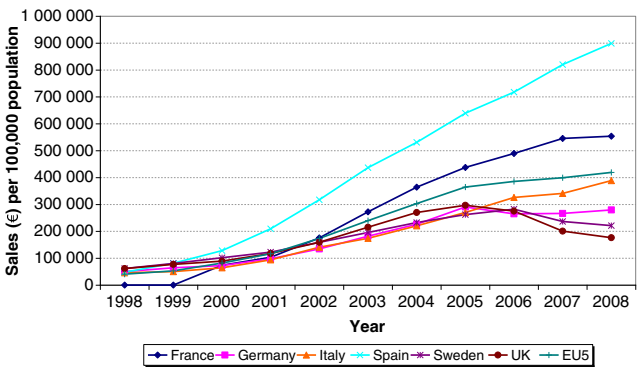
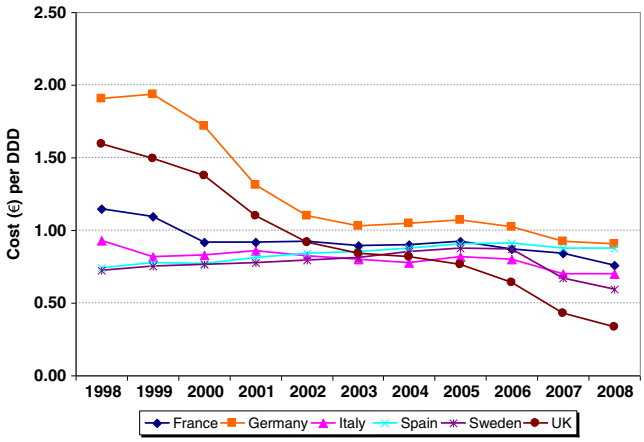


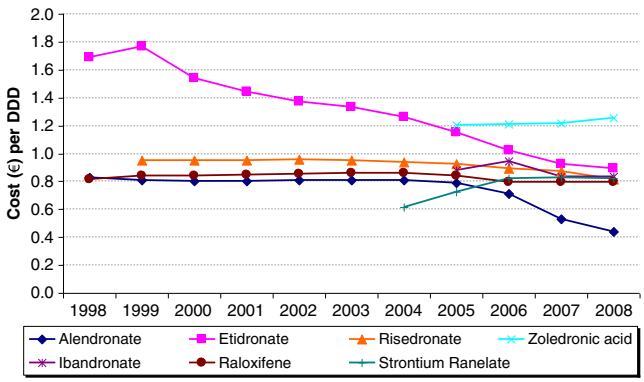
Fig. 41 Cost (€) per DDD in EU5 and Sweden all drugs



The average cost per DDD per treatment in EU5 is shown in Fig. 42. The price of etidronate has decreased continuously since 1998. There is an apparent drop in the price of alendronate in 2006 when generic substitutes were introduced (from 2003 in Sweden). Risedronate and raloxifene seem to have had a smaller reduction in price in recent years whereas zoledronic acid showed a slight increase.

The volume (DDDs) has increased linearly whereas the price per DDD has decreased or remained stable (varying between countries). Thus, it appears as if the price of the drugs has not had any major impact on total volume.

Fig. 42 Cost (€) per DDD per treatment in EU5



5.3.2 Uptake of treatments

Treatment uptake is presented using the following analyses:

The population coverage, i.e. the estimated proportion of the population 50 years or older that could be treated based on sales data adjusted for suboptimal adherence (as described in section 1.1.1).

DDD per 100,000 based on whole population (all ages and both genders)

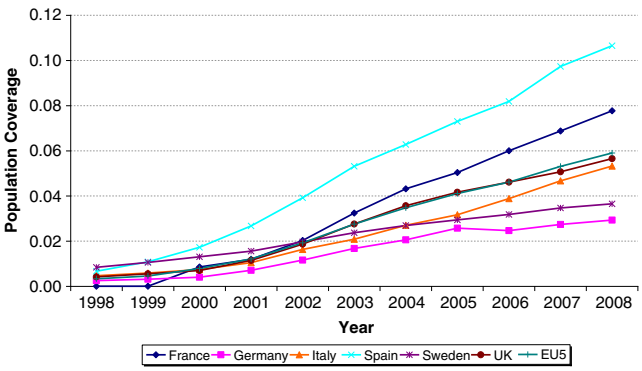
Estimated potentially treated patients compared to total patients assumed to be eligible for treatment

We first present the uptake of all drugs aggregated per country and then the uptake of the individual drugs where the proportion of patients potentially treated are presented.

5.3.2.1 Uptake of treatments aggregated

The estimated population coverage (Fig. 43) has increased with a fairly linear trend in all countries but at different rates. In 2008, the coverage was 7.8%, 2.9%, 5.3%, 10.7%, 3.7% and 5.7% for France, Germany, Italy, Spain, Sweden and the UK, respectively. Spain appears to have the fastest uptake and also has the highest coverage. In fact, Spain has a potential population coverage which is about 40% higher than France (the second highest uptake) and three times the uptake compared with Germany (the lowest uptake). The level of the estimated population coverage contrasts to the fracture risks in the different countries where Spain and Italy typically are considered countries with low fracture risk and Sweden and UK to be a high fracture risk countries. One part of the explanation for the uptake differences may be related to parallel import/export which could not be fully controlled for in the data. Even though no official information is available, Spain is traditionally considered to be a country with a high level of parallel export.

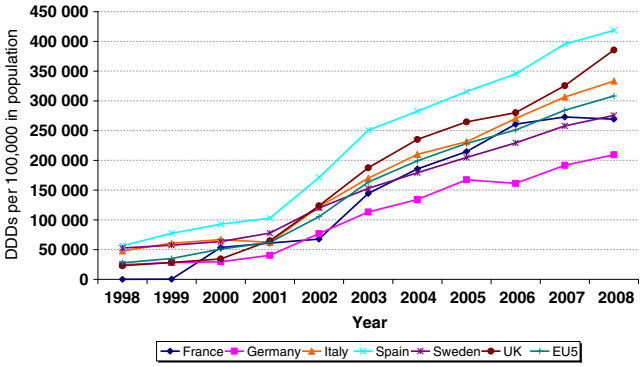
Fig. 43 Estimated proportion of population 50 years or older treated



5.3.2.2 Uptake of individual treatments

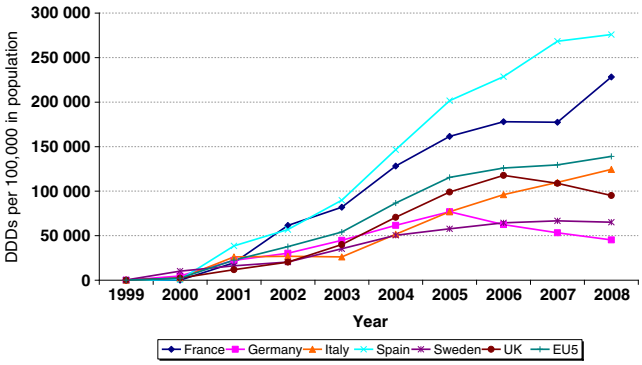
The uptake of specific treatments is shown in Figs. 44 to 52. The uptake of alendronate over time (Fig. 44) was more or less linear in all countries. A possible exception was France where the uptake seems to plateau from year 2006. The introduction of generic alendronate did not appear to be associated with an increase in the rate of uptake in the number of patients treated. In 2008, the rank order of uptake was Spain, UK, Italy, Sweden, France and Germany.

Fig. 44 Uptake of alendronate



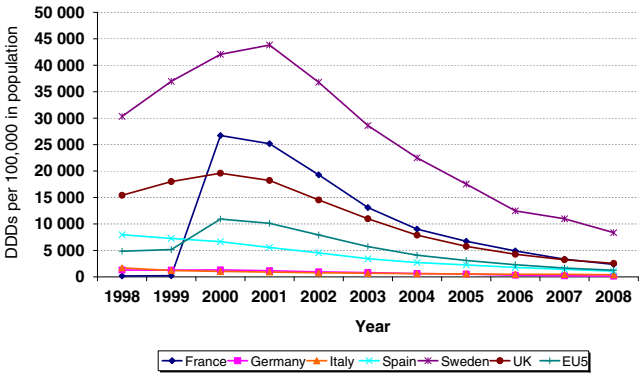
The pattern of the uptake of risedronate (Fig. 45) is not as clear as for alendronate and varied more widely between countries over time. The uptake has increased consistently in France and Italy whereas there is a notable reduction in sales in Germany (year 2005) and UK (year 2006). In 2008, the rank order of uptake was Spain, France, Italy, the UK, Sweden and Germany.

Fig. 45 Uptake of risedronate



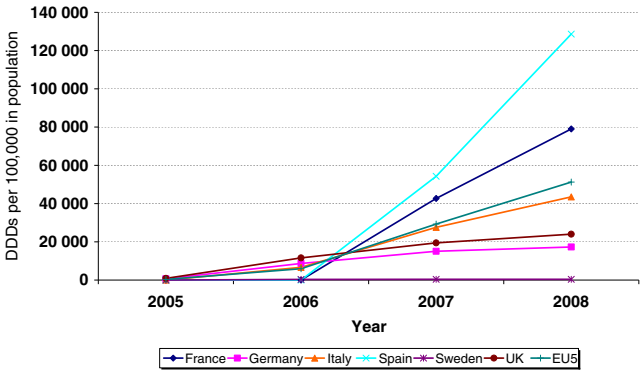
The uptake of etidronate (Fig. 46) has decreased to very low levels. This downturn in usage of etidronate can be explained by better clinical evidence for alendronate and other later marketed drugs in reducing fracture rates compared with the data available for etidronate.

Fig. 46 Uptake of etidronate



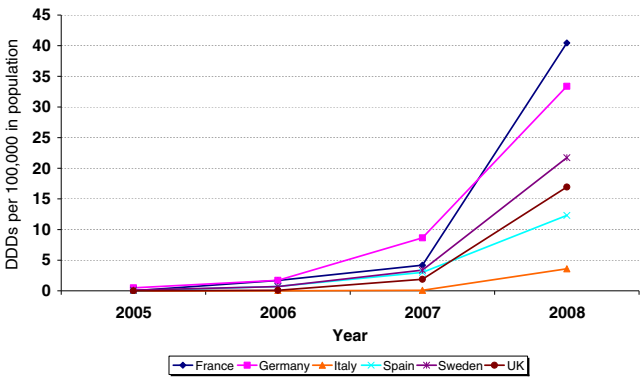
The uptake of ibandronate (Fig. 47) differs somewhat between the countries with the highest uptake in Spain and the lowest in Germany. In France, the Health agency (Haute Autorité de Santé (HAS)) HAS has recommended that ibandronate should no longer be reimbursed because of insufficient data on efficacy compared to other bisphosphonates. Ibandronate is not available for treatment of osteoporosis in the Swedish market.

Fig. 47 Uptake of ibandronate



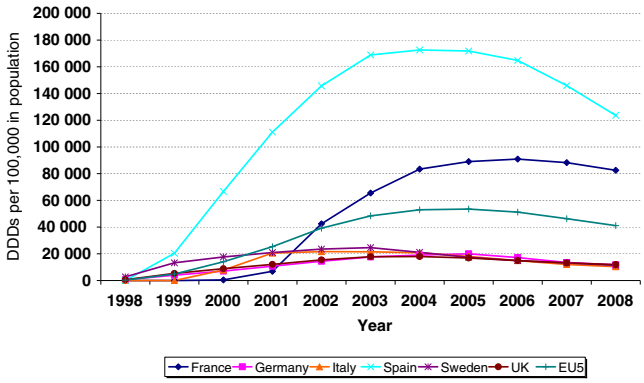
The uptake of zoledronic acid (Fig. 48) has been modest in all countries in terms of volume, however, there seems to be an increase in the rate of uptake from year 2007. In 2008, France had the highest usage followed by Germany, Sweden, the UK, Spain and Italy.

Fig. 48 Uptake of zoledronic acid



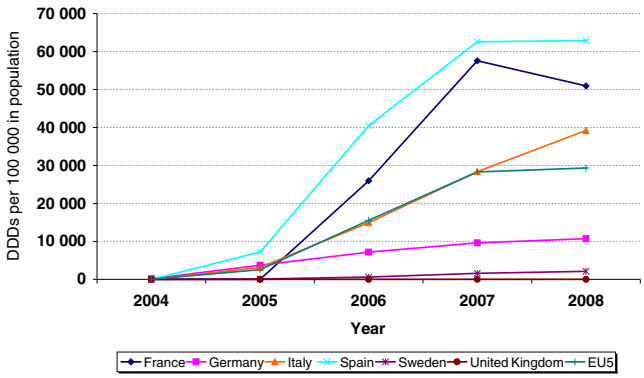
The uptake of raloxifene (Fig. 49) follows the same trend in the different countries, albeit at different usage levels, namely an initial increase in the uptake followed by an apparent decline. In 2008, the highest uptake is observed in Spain followed by France. In the other countries the uptake is almost at a similar level.

Fig. 49 Uptake of raloxifene



As for several of the other treatments, the uptake of strontium ranelate (Fig. 50) is highest in Spain and France. However, in these two countries the uptake increased rapidly from market introduction but seems to have levelled off from 2007. The marked decrease in uptake in France 2007 may be related to concerns regarding drug rash with eosinophilia and systemic symptoms (DRESS) side effects. The low uptake in Sweden could be related to a restriction in the indication to treat with strontium ranelate towards more severe osteoporotic patients.

Fig. 50. Uptake of strontium ranelate



The uptake of teriparatide and PTH (1–84) are shown in Fig. 51 and Fig. 52. Teriparatide is the most widely used of the two PTH drugs. In Spain, the uptake of teriparatide is the highest and has increased at a steady rate whereas in the other countries the uptake has been slower. In Spain, France, Italy and the UK the uptake increase in a fairly linear manner. In Germany, uptake seems to have stabilised and in Sweden the usage started to decrease from 2005.

Fig. 51 Uptake of teriparatide

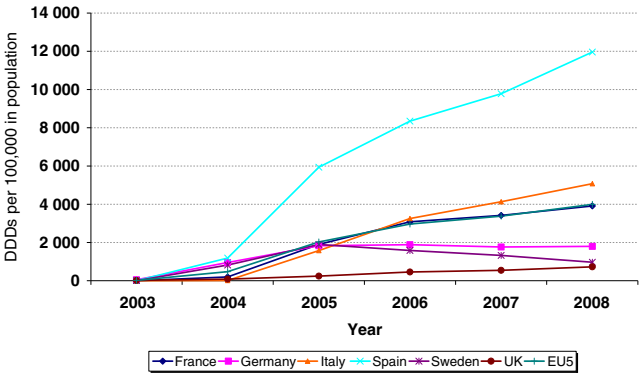
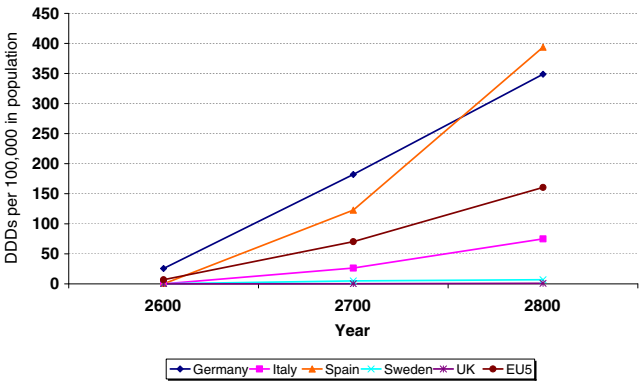


Fig. 52 Uptake of PTH (1–84)

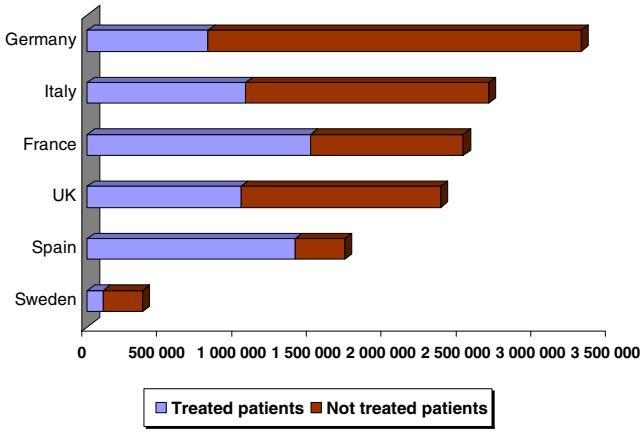


5.3.2.3 Proportion of patients treated

Fig. 53 shows the number of women that could be treated for a full year given the sales 2008 and adjusted for suboptimal adherence related to the number of women that could be assumed to be eligible (exceeding the fracture risk threshold) for an osteoporosis treatment. One minus the ratio between treated patients and all patients can be viewed as an approximation of the treatment gap. The treatment gap varies between countries which is a reflection of the sales as outlined above and national differences in fracture risk between countries. Spain, for example, was shown to have the highest treatment uptake, a relatively low risk of fracture in the population and the smallest gap (about 19% for women) compared with Sweden which has one of the highest levels of population fracture risk and an estimated treatment gap for women of 71%.

Table 58 shows the same information as in Fig. 53 in numbers and with the estimated treatment gaps. In total for all six countries there are 12.95 million women that exceed the fracture risk level for treatment and 45% of these women could potentially be treated based on the sales data.

Fig. 53 Estimated treated women compared to total female population above 50 years assumed to be eligible for treatment (year 2008)



The calculations for men (Fig. 54 and Table 58) indicate that the volume of sold osteoporosis drugs would be sufficient to cover treatment for more patients than the number that fall above the fracture risk threshold in France, Spain and the UK. Note, however, that the results from this analysis has to be handled with some caution since we have assumed the same distribution of drug use between genders as observed in Sweden. Also, the analysis assumes that treatments are currently targeted appropriately. In total for all six countries there are 1.45 million men that exceed the fracture risk level for treatment and 78% of these men could potentially be treated based on the sales data (Table 58).

Fig. 54 Estimated treated men compared to total male population above 50 years assumed to be eligible for treatment (year 2008)

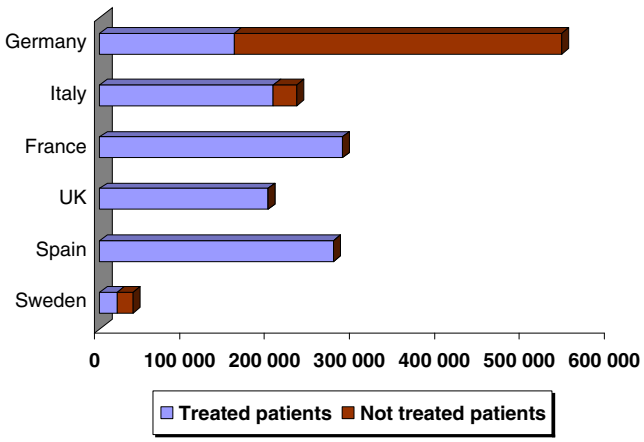


Table 58 Number of men and women (in thousands) above 50 years exceeding the fracture risk threshold for treatment and the potential number treated

	Number potentially treated (000)	Number exceeding fracture risk threshold (000)	Difference (000)	Treatment gap (%)
Women				
Sweden	106	368	262	71%
Spain	1,391	1,722	331	19%
UK	1,028	2,363	1335	56%
France	1,492	2,514	1022	41%
Italy	1,062	2,684	1622	60%
Germany	809	3,301	2492	75%
Total	5,890	12,952	7062	55%
Men				
Sweden	21	40	19	48%
Spain	275	238	-37	-16%
UK	198	119	-78	-66%
France	286	283	-2	-1%
Italy	204	231	27	12%
Germany	158	543	385	71%
Total	1,141	1,454	313	22%

5.3.2.4 A comparison of data from the Swedish prescribed drug register and sales data

The Swedish Prescribed Drug Register was established in June 2005. It contains all filled prescriptions outside of the hospital setting dispensed by pharmacies for the whole Swedish population. The loss of patient information from non-hospital prescriptions in the Swedish Prescribed Drug Register is at maximum 0.6%. Aggregated information separated on age and gender for all drugs is available from 2006 until 2009 on the website of National Board of Health and Welfare (www.sos.se). Information regarding the number of patients prescribed a treatment, total number of DDDs, DDDs per 1,000 in population, and total number of prescriptions can be extracted. In the following tables and figures we present an analysis based on prescription data for osteoporosis drugs extracted from this source and a comparison with the IMS Health data.

As can be seen in Fig. 55 and Table 59 the IMS Health sales data on volume (converted from mg to DDDs) matches well with the Swedish prescription register for non-bisphosphonates but less so for bisphosphonates. The main part of the gap is related to a difference in the use of alendronate (Fig. 56).

The IMS Health sales data shows an estimated DDD per 100,000, which is about 20% higher than what was dispensed through Swedish pharmacies. Overall, the IMS Health data show higher DDDs per 100,000 in the population compared with the prescription data. The

explanation of this discrepancy between the register and sales data is not self-evident. One part of the explanation for the uptake differences could be related to parallel import/export or to prescriptions filled through hospital pharmacies which were not captured in the Swedish prescription register. However, the parallel export in Sweden is very limited accounting for about 1-2% of total sales[1] and only 1-2% of all alendronate prescriptions are filled in an inpatient care setting.[2] Also, notable is that there seems to be a plateau or, even a decrease, in the uptake of alendronate in 2009 where the number of DDDs per 100,000 started to decrease (Fig. 56).

Fig. 55 DDDs per 100,000 in population for bisphosphonates based on the Swedish Prescribed Drug Register and IMS Health data

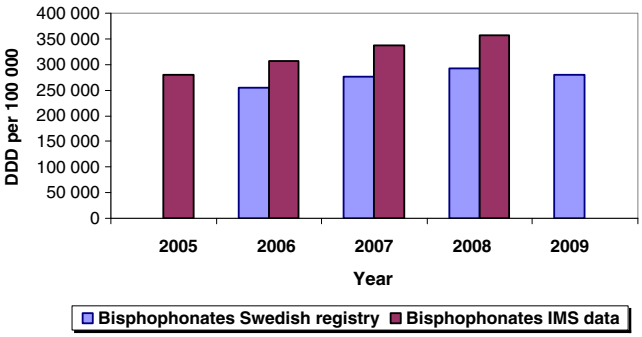
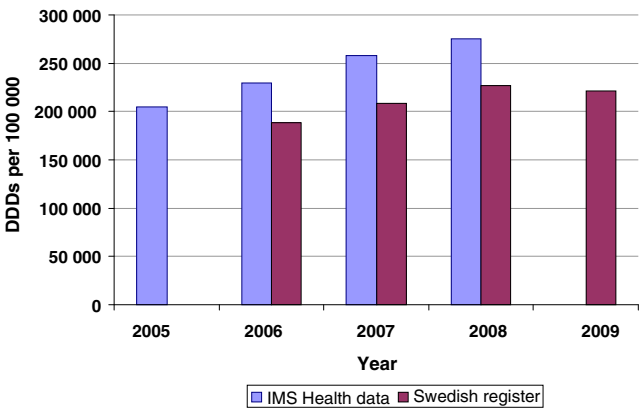


Table 59 DDDs per 100,000 in population for non-bisphosphonates based on the Swedish Prescribed Drug Register and IMS Health data

	Bisphosphonates		Raloxifene		Strontium ranelate		PTHs	
Year	Swedish register	IMS Health data	Swedish register	IMS Health data	Swedish register	IMS Health data	Swedish register	IMS Health data
2005	-	280,057	-	17,400	-	-		1,893
2006	253,984	306,371	14,806	14,928	539	606	1,558	1,583
2007	275,888	336,727	13,008	13,182	1,464	1,600	1,340	1,327
2008	291,949	356,923	11,126	11,370	2,003	2,128	1,034	972
2009	280,060	-	9,425	-	2,338	-	770	-

Fig. 56 DDDs per 100,000 in population for alendronate based on Swedish prescription register and IMS Health data



As can be seen in Fig. 57, the percentage of the population filling a prescription increases with age. In women it rises from 0.7% in the age interval 50–54 years up to 11.3% in the 80–84 year age group and thereafter it decreases at ages above 85 years. Men follow the same pattern but at much lower levels. The peak uptake (2.1%) is reached in the 80–84 year age group.

The annual number of patients that filled a prescription for an osteoporosis drug increased by about 10,000 between years 2006 and 2009 (Table 60). About 87% of all patients treated were women. These figures can be compared to the estimate of how many patients could be treated for a full year based on the IMS Health data. For 2008, the number of patients was estimated at 127, 025 which is 24% higher than the actual number of patients that filled a prescription based on register data. In Table 61, the treatment gap is shown in Sweden for men and women at different ages based of the number of patients that filled an osteoporotic drug prescription in year 2009. The table shows the proportion of the population exceeding the

[0] This estimate was provided by Tamro, one of the largest Swedish pharmaceutical wholesalers

[0] Information provided by Apotekens Service AB

fracture risk threshold for treatment that might receive treatment according to gender and age groups. The treatment gap decreases with age for both ages. For women the treatment gap is 95% in the 50–54 year age group and is at lowest (43%) between 80–84 years of age. Since these treatment gap calculations are based on the actual number of patients that have filled a prescription they are better estimates than those based on sales data in the previous section. Based on sales data (see Table 58) the treatment gap over all ages above 50 years was 71% and 48% for women and men, respectively. This can be compared to the higher estimates of the treatment gap of 75% for women and 67% for men based on the number of patients filling a prescription.

Fig. 57 Percentage of population prescribed an osteoporotic drug in Sweden according to age group

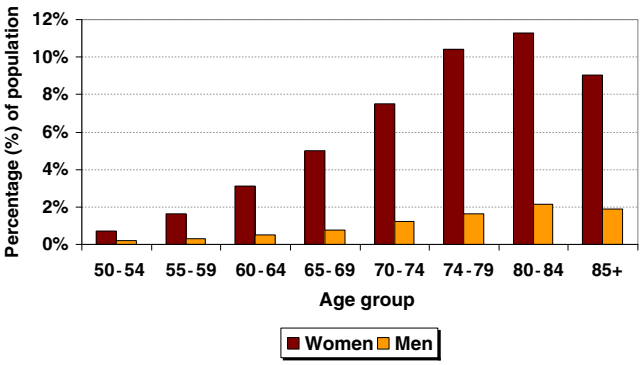


Table 60 Number of patients aged 50 years or more prescribed an osteoporotic drug in Sweden

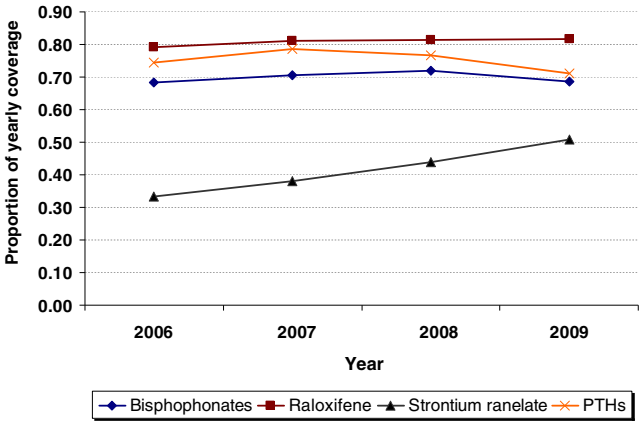
	Bisphosphonates		Raloxifene		Strontium ranelate		PTHs	
Year	Women	Men	Women	Men	Women	Men	Women	Men
2006	79,694	11,014	4,619	0	399	14	500	9
2007	84,343	11,883	3,983	2	951	41	404	10
2008	87,829	12,769	3,412	1	1,139	44	319	10
2009	88,918	13,113	2,909	0	1,165	48	250	12

Table 61 Number of patients that filled an osteoporotic drug prescription in year 2009 related to number in the population exceeding fracture risk threshold for treatment in Sweden according to gender and age groups

	Women			Men		
Age group	Number of patients prescribed an osteoporotic drug in 2009	Number exceeding fracture risk threshold	Treatment gap (%)	Number of patients prescribed an osteoporotic drug in 2009	Number exceeding fracture risk threshold	Treatment gap (%)
50-54	2,140	47,232	95%	563	7,670	93%
55-59	4,732	54,150	91%	926	6,336	85%
60-64	9,872	63,240	84%	1,660	5,871	72%
65-69	12,621	61,712	80%	1,952	5,502	65%
70-74	14,609	45,571	68%	2,157	5,580	61%
74-79	17,674	38,243	54%	2,223	4,752	53%
80-84	16,652	29,376	43%	2,148	2,688	20%
85+	14,894	28,678	48%	1,544	1,343	-15%
Total	93,194	368,202	75%	13,173	39,742	67%

Fig. 58 shows the proportion of a year that a patient on average has access to a daily dose of treatment based on the volume of filled prescriptions. This is calculated by dividing the total DDDs prescribed by 365 and the number of patients that filled a prescription. The observed coverage gap encompasses both treatment gaps (compliance) and treatment discontinuation (persistence). Raloxifene has the highest coverage followed by PTHs and bisphosphonates. The larger gap observed for strontium ranelate can partly be explained by that the uptake has not reached a steady state but is rising due to its relatively recent market introduction (approved in Sweden for reimbursement mid-year 2005). Also, the coverage decreased somewhat in year 2009 for PTHs and bisphosphonates.

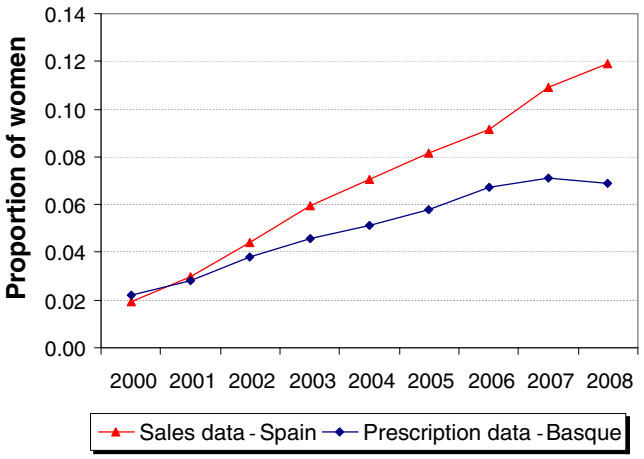
Fig. 58 The average proportion of a year that a patient has access to a daily dose of treatment based on the volume of filled prescriptions



5.3.2.5 A comparison of prescription data from the Basque region in Spain and sales data

In a recent publication by Etxebarria-Foronda et al. [3] the use of osteoporosis treatments in the Basque region in Spain was analysed. In this study they derived data on the total annual number of DDDs of osteoporosis treatments prescribed to women in Basque between 2000 and 2008. The source of the data used is unfortunately not made clear in the article. Based on the DDD data they estimated the number of women above 54 years of age that could be treated for a full year (i.e., no adjustments for suboptimal adherence was made). Fig. 59 shows a comparison between the estimated proportion of women that could be treated in Basque compared to the sales data for the whole of Spain. The same pattern was observed in this comparison as with the Swedish Prescribed Drug Register comparison, i.e., the sales data showed a much higher uptake than local prescription data. The difference also seemed to increase over the years. This comparison needs to be interpreted with some caution since the prescription data only cover a part of Spain and the publication does not disclose what medications are included or the source of the information.

Fig. 59 Proportion of women in the population that could be treated for full year based on Basque prescription data and IMS Health sales data for Spain [3]



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6 The future burden of fractures and the consequences of increasing treatment uptake

Summary

The objectives of this chapter were to estimate how the expected demographic changes will impact the burden of disease up to 2025 in terms of fractures, morbidity and costs in the EU5+ and how an increased treatment uptake would affect the burden.

The key messages of this chapter are:

This chapter projects the burden in terms of number of fractures, morbidity and costs between 2010 and 2025.

The annual number of fractures in the EU5+ was estimated to increase from 2.46 million in 2010 to 3.17 million in 2025 (a total increase of 28.9%).

The number of QALYs lost annually due to fractures was projected to increase from 0.85 million to 1.0 million over the same time period.

The total monetary burden in the EU5+ was estimated to increase from €30.7 billion in 2010 to €38.5 billion in 2025.

Increasing treatment uptake to provide all individuals with a 10-year probability of fracture exceeding that of an age- and sex-matched individual with a previous fracture with a 3-year treatment would require a 2.4-fold increase in provision of treatment in the EU5.

A large proportion of all fractures occur in osteopenic patients, and pharmacological treatment given to high risk patients will thus only partially alleviate the increased burden, which in our estimation was solely caused by demographic changes.

Increasing treatment uptake in the EU5+ would result in 95,000 fewer fractures and 33,357 QALYs gained annually in 2025.

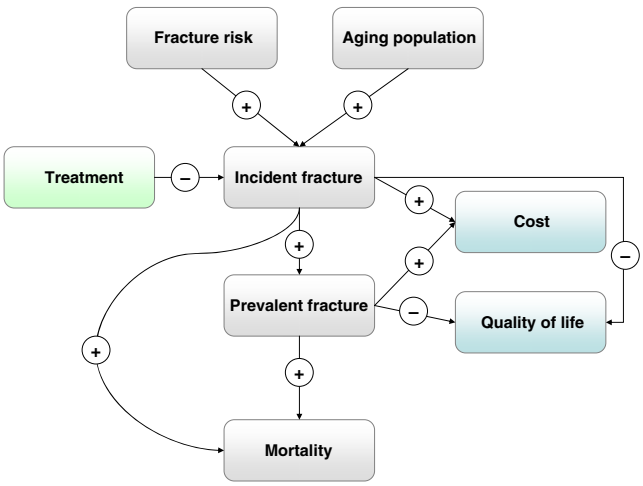
The accumulated number of potentially avoided fractures from increasing uptake up to 2025 was estimated at 699,000.

13% of the projected increase in fractures and 20% of the projected increase in lost QALYs could cost-effectively be avoided by increasing treatment uptake to encompass all individuals with a 10-year probability of fracture exceeding that of an age- and sex-matched individual with a previous fracture.

6.1 Introduction

The prevalence of osteoporosis, as judged by BMD measurements, increases markedly with age. Approximately 6% of women and 2.5% of men in the developed world have osteoporosis at the age of 50 years, and this proportion rises steeply with age to reach approximately 50% and 20% in those older than 85 years (Chapter 3). Approximately 12 million women and 3 million men between 50–85 years have osteoporosis in the EU5. In women aged 50 years, the remaining lifetime risk of experiencing a major osteoporotic fracture ranges from 26% in Spain to 49% in Sweden. Fig. 60 gives a simple schematic overview of the determinants of the burden of osteoporotic fractures. The total fracture risk in a population will depend on its underlying age-specific fracture risk, the age-distribution, and what measures are taken to reduce the risk of fractures. The consequences of a fracture can be divided into an acute phase where costs, lost QoL and mortality are considerable and a long-term phase where an effect on morbidity and costs persists, but is less pronounced [1–4].

Fig. 60 Overview of the determinants of the burden of osteoporotic fractures



The objective of this chapter was 2-fold. The impact of the demographic changes on the burden up to 2025 in terms of fractures, morbidity, and costs in the EU5+ was estimated. Furthermore, it was estimated how an increased treatment uptake would affect the burden up to 2025 in terms of fractures, morbidity and costs in the EU5+.

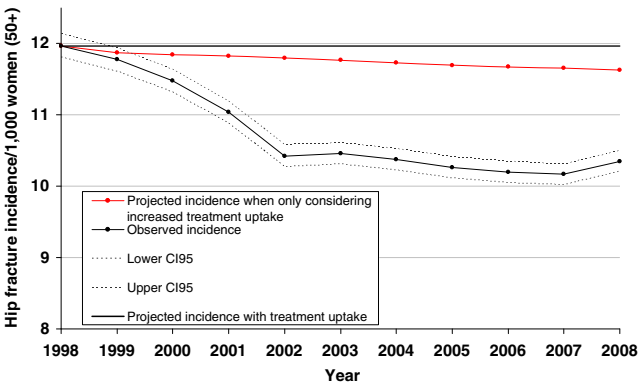
6.2 Secular trends

The number of fractures has increased during recent decades, partly because of an increasing number of elderly women in society. Over and above this, there have been changes over time in the age- and sex-specific

risk of fracture, most completely studied in the case of hip fracture [5, 6]. Whilst Swedish crude hip fracture incidence has increased, age-adjusted incidence (independent of demographic trends) has recently remained stable between 1967 and 2001. Palvanen et al. [7] report a clear rise in the rate of humeral fractures in Finnish women 60 years of age and older from 1970 till late 1990s followed by stabilisation or even decreased fracture rates in later years. The precise reasons for secular changes are unknown, but a cohort effect towards improved functionality among older women and actions and interventions in preventing falls and minimising fall severity cannot be ruled out. These findings are supported by a recent Canadian population-based analysis, which found that the age-adjusted incidence of low-trauma fractures has shown an annual decrease between 1986 and 2006 of 1.2% and 0.4% in women and men, respectively [8]. Furthermore, studies from the UK [9] and Germany [10] have reported a stabilisation of age-standardised hip fracture incidence rates over the periods 1989–1998 and 1995–2004, respectively. Few studies are available from Southern Europe. A Spanish study reported that the number of hip fractures increased between 1988 and 2002, but no significant change was observed in age-adjusted incidence rates among men or women, over the same period [11].

We found similar trends as in previous studies when analysing Swedish crude hip fracture incidence between 1998 and 2008 from the Swedish patient register. Fig. 61 shows a declining incidence of hospital discharges with s72.x (fractures of the hip and femur) as the primary ICD-10 diagnosis for hospitalisation. The observed fracture rates were based on a total of 207,000 fractures in 19.2 million person-years in Swedish women older than 49 years. The observed incidences were not adjusted for changes in demography. The red line in Fig. 61 represents a projected incidence from 1998 that takes account of the increase in uptake of treatment between 1998 and 2008. Treatment was assumed to reduce the risk of hip fractures by 38% [12] and treated patients were assumed to have a 2-fold underlying risk of fracture compared with the general population. This projection can be compared with the extrapolated incidence of 1998 which disregards treatment uptake and secular trends, represented by the flat black line. Comparison of the area between these two curves with the area between the observed incidence curve and the flat incidence curve suggests that approximately 16.5% of the observed risk decline between 1998 and 2008 could potentially be attributed to antifracture treatment. It is also relevant to note that the age- and sex-specific incidence of hip fracture appears to have remained unchanged from 2002.

Fig. 61 Observed and projected risk of hip and femur fractures (s72.x) between 1998 and 2008



Treatment penetration was only marginal during those years when reductions in age-adjusted risks were first observed. It is therefore unlikely that increased access to treatment is the major cause behind these trends of stabilising or decreasing age-adjusted risks. Furthermore, a majority of all fragility fractures occur in individuals with a T-score above −2.5 SD and fracture prevention targeted at individuals at high risk of fracture will thus have a limited impact on the total fracture burden.

The findings presented above points at a stabilisation of fracture rates the past decades and therefore, for the purpose of this report, a constant age- and sex-specific incidence was used for future fracture rate projections.

6.3 Demography

Irrespective of whether age-adjusted risks are decreasing or not, the expected demographic changes will be associated with an increase in the number of fractures in Western Europe during the coming 15 years. As described in the previous chapters, age is an important and independent clinical risk factor for fracture and the number of elderly men and women is projected to increase (Fig. 62 and Fig. 63). Estimates based on United Nations World Population Prospects data [13] indicate that the number of women and men older than 50 years will increase in the six reference countries. Particularly noteworthy is the group of women and men older than 89 years, which, depending on country, is projected to increase 1.5 to 3-fold in size in 2025. The proportion of the population older than 65 years is projected to increase from 14% to 17% between 2010 and 2025 in the EU5 and Sweden (Table 62).

Fig. 62 Changes (%) in the number of women by age and country between 2010 and 2025 by country

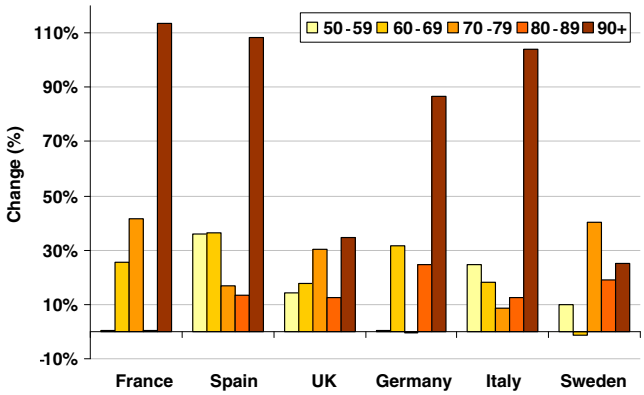


Fig. 63 Changes (%) in the number of men by age and country between 2010 and 2025

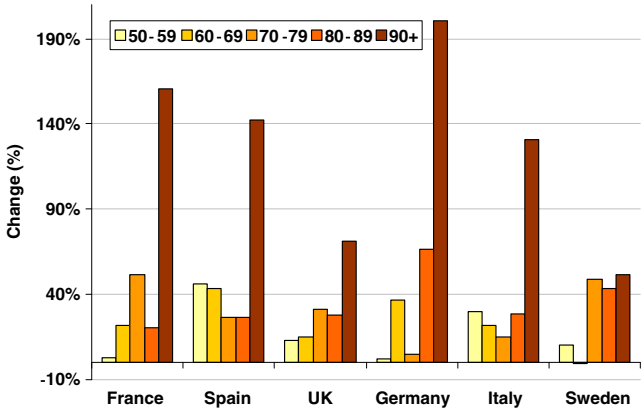


Table 62 Total population (in thousands) and projected proportion of total population older than 65 years in the EU5 and Sweden (%)

	2010	2015	2020	2025
	Total population (000)			
France	62,634	63,899	64,930	65,767
Spain	82,056	81,345	80,422	79,258
UK	60,098	60,604	60,408	60,020
Germany	45,317	47,202	48,564	49,266
Italy	61,899	63,529	65,088	66,601
Sweden	312,004	316,579	319,412	320,912
All	59,398	64,375	69,016	74,390
	Age 65+ years (% of total population)			
France	16.1	17.9	19.7	21.4
Spain	16.3	16.9	17.7	19.2
UK	15.6	16.7	17.5	18.3
Germany	19.3	20.3	21.7	23.6
Italy	19.4	20.6	21.8	23.1
Sweden	17.2	18.8	19.9	20.6
All	19.0	20.3	21.6	23.2

The proportion of the population aged 65 years or older in Europe is expected to grow and the clinical and financial burden of osteoporosis is consequently also expected to increase over time. Although the epidemiology of fractures (particularly hip fractures) and the prevalence of osteoporosis are relatively well documented, limited data are available on the burden of osteoporosis and fractures at a national level, and potential trends over time. The future burden of osteoporosis, set to increase in the coming years due to changing demography, could potentially be decreased by closing the "treatment gap", i.e., the difference between current treatment uptake and the number of patients that, according to certain criteria, should be treated.

6.4 The treatment gap

Criteria for eligibility for treatment vary according to national guidelines in different countries (see Chapter 2). A commonly used definition of osteoporosis has been a femoral neck or lumbar spine T-score at or below -2.5 SD. Patients who also have a prevalent fracture are considered to have established osteoporosis [14]. If the proportion of the population with a T-score at the femoral neck at or below -2.5 SD is considered as an intervention threshold, the current level of treatment penetration is low in many countries. When reference BMD values from NHANES III [15] are used, then 6%, 12%, 22%, and 36% of women aged 50, 60, 70, and 80 years will have a T-score <−2.5 SD in a given population. These estimates are in good agreement with empirical data from different regions of the world [14]. Applying such calculations to the UK population indicates that approximately 2.4 million women have a T- score <−2.5 SD. Age-specific numbers for other countries are given in Table 23 in Chapter 3.

These numbers can be compared to the current estimate of treatment. In the UK, for example, approximately one million women can receive treatment based on sales data (see Chapter 5). Thus, assuming that only patients with osteoporosis are treated, then only 41% of women with osteoporosis as defined by BMD are treated. In practice, the proportion treated is expected to be less, since an uncertain proportion of treatments will be given to women without osteoporosis. Estimates for men and men and women in other countries are given in Table 63 and Table 64.

Table 63 Number (in thousands) of women aged 50 years or more with osteoporosis in EU5 and Sweden using female-derived reference ranges at the femoral neck and the number of patients being treated

	Population (000)	% of population treated*	Population with T-score <−2.5 SD (000)	Number treated (000)*	% of osteoporotic population potentially treated
France	12,447	12.0	2,817	1,492	53
UK	11,562	8.9	2,545	1,028	40
Germany	17,797	4.5	4,034	809	20
Italy	12,989	8.2	3,051	1,062	35
Spain	8,513	16.3	1,937	1,391	72
Sweden	1,832	5.8	411	106	26
All	63,308	9.1	14,385	5,783	40

*Assuming that women receive 87% of all prescribed treatments

Table 64 Number (in thousands) of men aged 50 years or more with osteoporosis in EU5 and Sweden using female-derived reference ranges at the femoral neck and the number of patients being treated

	Population (000)	% of population treated*	Population with T-score <−2.5 SD (000)	Number treated (000)*	% of osteoporotic population potentially treated
France	10,318	2.8	694	286	41
UK	10,030	2.0	673	198	29
Germany	15,195	1.0	997	158	16
Italy	10,710	1.9	745	204	27
Spain	7,200	3.8	492	275	56
Sweden	1,645	1	112	21	18
All	53,453	2.1	3,600	1,120	31

*Assuming that men receive 13% of all prescribed treatments

The development of FRAX has changed the manner of targeting treatment from that based on BMD to that based on fracture probability (see Chapter 3) [16]. The UK, Sweden and Germany have developed guidelines based on fracture probability. In the UK, intervention is recommended in women with a prior fragility fracture and in men and women with an age-specific fracture probability that corresponds to a women with a previous fracture (no other CRFs, an average BMI and without BMD) [17–19].

Using intervention thresholds based on the absolute fracture probability corresponding to an age-matched woman with a prevalent fracture allows calculation of how many individuals who may be at a sufficient risk to be treated (see Fig. 21 and 22 in Chapter 3). In all, 12.6 million women and 1.4 million men in the EU5 fall above the threshold probability for treatment. However, it does not provide guidance for how much a country's treatment uptake should be increased. Even though long-term pharmacological fracture prevention is relatively safe [20] it would be unrealistic to imagine that all patients at sufficiently high risk would be treated for the remainder of their life. Thus, to estimate a "target treatment uptake" based on the intervention thresholds assessed using the translational approach (see Chapter 3 for more detail), the following assumptions were made:

- Every individual who meets or exceeds the absolute risk threshold should receive a treatment that, on average, will last for 3 years. It was implicitly assumed that an individual can be given additional treatments later in life.
- Based on summary prescription data from Sweden (www.socialstyrelsen.se) it was assumed that 13% of all doses were prescribed to men in all index countries. This figure is in close agreement with findings from Norway where 10% of users were men [21].
- The current number of possibly treated individuals was derived from sales data (Chapter 5). The estimates were not adjusted for adherence because it is unknown how adherence will change in the future and a given amount of consumed doses should anyway translate into avoided fractures, irrespective of adherence on the patient level. Therefore, all estimates in tables and figures from here onwards in this report reflect person-years with treatment rather than number of treated individuals and may thus differ from some estimates presented in Chapter 5.
- It was assumed that the "target treatment uptake" will be reached by 2025. Treatment uptake was assumed to increase linearly. The treatment uptake observed from sales data for 2008 were assumed to be the same for 2010, where the projection starts.

Even were treatment uptake to remain on the levels currently seen in sales, the number of women and men treated would still increase up to 2025 due to demographic changes (Table 65 and Table 66). The estimated target uptake corresponded to an average increase in the number of prescriptions in the EU5 by a factor of 2.36 when demographic changes were accounted for.

Table 65 Number of person-years with treatment in women 2010–2025 with current and target uptake

		2010	2015	2020	2025
Spain	Current treatment uptake	1,015,749	1,111,203	1,215,128	1,325,974
	Approaching target uptake	1,015,749	1,143,456	1,285,668	1,441,436
	Difference	0	32,253	70,539	115,461
Sweden	Current treatment uptake	77,703	81,224	85,253	88,773
	Approaching target uptake	77,703	132,946	193,830	258,363
	Difference	0	51,722	108,576	169,590
Germany	Current treatment uptake	590,802	632,863	667,255	673,861
	Approaching target uptake	590,802	1,212,993	1,890,567	2,526,996
	Difference	0	580,130	1,223,312	1,853,136
Italy	Current treatment uptake	775,194	827,653	880,829	927,559
	Approaching target uptake	775,194	1,221,102	1,718,283	2,250,383
	Difference	0	393,448	837,454	1,322,824
UK	Current treatment uptake	750,739	804,438	857,682	894,498
	Approaching target uptake	750,739	1,083,126	1,451,949	1,824,163
	Difference	0	278,688	594,268	929,665
France	Current treatment uptake	1,089,450	1,171,288	1,239,034	1,297,415
	Approaching target uptake	1,089,450	1,442,562	1,812,962	2,198,869
	Difference	0	271,273	573,927	901,454

Table 66 Number of person-years with treatment in men 2010–2025 with current and target uptake

		2010	2015	2020	2025
Spain	Current treatment uptake	200,716	224,439	251,536	281,588
	Approaching target uptake	200,716	228,648	260,969	297,427
	Difference	0	4,208	9,433	15,839
Sweden	Current treatment uptake	15,079	16,014	17,013	17,746
	Approaching target uptake	15,079	16,487	18,018	19,318
	Difference	0	473	1,005	1,572
Germany	Current treatment uptake	115,301	126,949	136,138	137,800
	Approaching target uptake	115,301	268,511	439,757	598,788
	Difference	0	141,563	303,619	460,988
Italy	Current treatment uptake	149,169	161,398	174,532	186,385
	Approaching target uptake	149,169	186,783	229,434	274,330
	Difference	0	25,385	54,902	87,945
UK	Current treatment uptake	144,222	155,452	166,064	172,606
	Approaching target uptake	144,222	141,127	135,457	124,888
	Difference	0	-14,325	-30,606	-47,718
France	Current treatment uptake	208,498	225,493	240,163	253,480
	Approaching target uptake	208,498	251,384	295,314	340,792
	Difference	0	25,891	55,150	87,313

The current treatment uptake and the suggested target treatment uptake (Fig. 64 and Fig. 65) will vary across countries based on the available sales data and the proportions of women and men exceeding the intervention threshold. Countries with a higher current treatment uptake (e.g. Spain) would only need to increase uptake of interventions by a small amount, whilst countries with lower current prescription rates like Germany and Sweden would have to increase treatment considerably to reach the "target treatment uptake". The number of men estimated to lie at or above the intervention threshold was relatively small (see Chapter 3) and only marginal increases up to 2025 in treatment provision to men was estimated for most countries. The target proportion of men receiving treatment in the UK was estimated to be even lower than the current treatment penetration (Fig. 65). The opposite was seen for Germany where the number of men treated would have to increase considerably for the "target treatment uptake" to be reached. These differences in target uptake between countries are caused by the fact that the differences in average 10-year probabilities of fracture between women and men are larger in the UK than in Germany. A smaller proportion of men in the UK will thus reach the threshold probability, which is defined as that of an age-matched woman with a prior fracture and no other risk factors.

Fig. 64 Percentage* of women older than 49 years treated with current (2010) and approaching target uptake (2025)

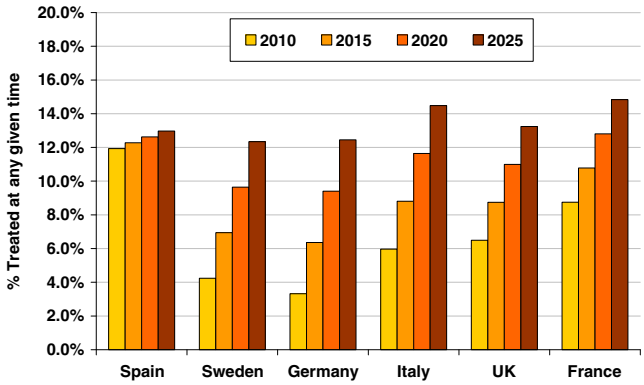
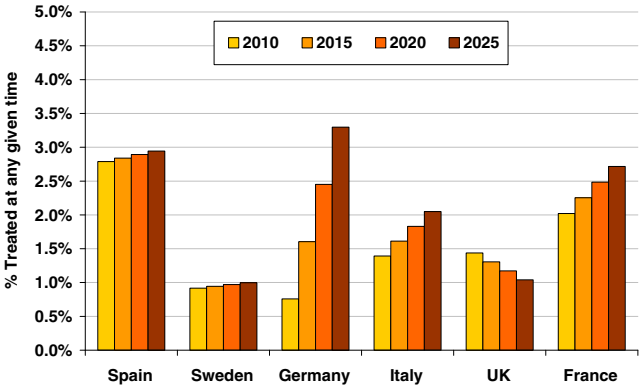


Fig. 65 Percentage* of men older than 49 years treated with current (2010) and approaching target uptake (2025)



The same model and data as in Chapter 4 to estimate the burden of fractures 2010 was used to make projections up to 2025 and to estimate the consequences if the "target treatment uptake" suggested above was reached. The model was run for one scenario with current treatment uptake and one scenario where treatment was linearly increased as shown in Fig. 66. The following assumptions were made when calculating the nation-wide effects on fracture rates, costs, mortality and morbidity.

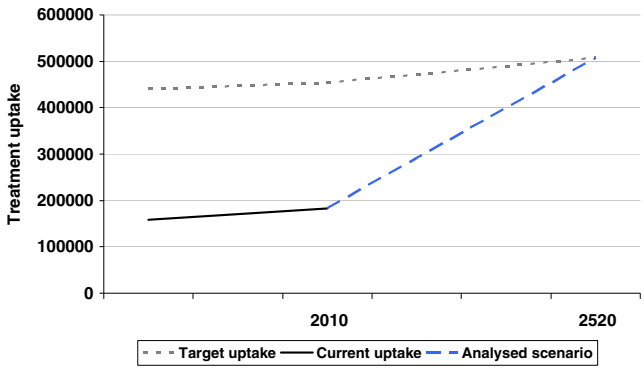
- Age-specific fracture rates were assumed to remain unchanged up to 2025.
- Demographic changes, as projected by United Nations World Population Prospects data [13], were used. Current treatment uptake was assumed to grow in parallel with the population in the scenario where no other change in treatment uptake up to 2025 was assumed.
- Each treated individual was assumed to have a relative risk of fracture twice that of the general population. This approximately corresponds to the excess fracture

risk in patients with a FRAX probability exceeding the intervention threshold risk compared with the general population.

- After stopping treatment each individual received a linearly declining residual antifracture effect equally long as the time on treatment [20, 22–24]. This means that when three years of treatment was stopped the effect declined to 0 over 3 years. In other words, a 3 year treatment conferred 1.5 years of "free" effect.
- The effects of alendronate estimated in a recent meta-analysis [12] were assumed to apply to all treatments used up to 2025. All treatments were thus assumed to reduce the risk of hip fracture (RR 0.62), clinical vertebral fracture (RR 0.56), wrist fracture (RR 0.85), and other fractures (RR 0.82).
- All countries were assumed to have a 80/20 mix of generic alendronate and second-line branded treatments.
- Each treatment was assumed to be associated with a physician visit each year and a BMD measurement every second year [25, 26].
- To allow interpretation and comparison over time no discounting of costs or QALYs was employed unless specifically stated.

A schematic representation of how the "target treatment" level is reached is shown in Fig. 66 where the current and target uptake rate are adjusted for demographic changes.

Fig. 66 Concept of closing the gap



The same data were used as for the calculation of the burden of disease in Chapter 4. The cost of the 20% second-line treatments was calculated from current local prices (Table 67).

Table 67 Unit costs for treatment and management (€, 2010)

	BMD measurement	Physician visit	Generic ALN (per year)	2nd line (per year)
Sweden	152[a]	130[a]	27[b]	443[b]
UK	51[c]	50[c]	18[d]	315[d]
France	41[e]	50[f]	209[j]	418[j]
Germany	36[e]	38[g]	245[k]	689[k]
Italy	81[e]	50[h]	294[l]	669[l]
Spain	109[e]	76[i]	201[m]	460[m]

[a] [27]
[b] www.fass.se [c] [28]
[d] British National Formulary
[e] [29]
[f] [30]
[g] [31]
[h] [32]
[i] [25]
[j] www.vidalpro.net
[k] www.rote-liste.de
[l] www.agenziafarmaco.it
[m] www.portalfarma.com

6.5 Results

6.5.1 Projection of fractures

The annual number of fractures (all types) is projected to increase from 2010 to 2025 with the current treatment uptake (Table 68). As is seen in Table 68 below this is also the case even if the "target uptake" is reached. For example, with the current treatment uptake the total number of fractures in France is estimated to increase from 379,493 in 2010 to 506,995 in 2025, a total increase of 33.6%. The increase will be mitigated (30.8%), but still substantial if the suggested "target uptake" is reached. In EU5 and Sweden, the number of fractures (all types) is projected to increase by 28.9% between 2010 and 2025 (from 2.46 million to 3.17 million). This is due to the population increase and demographic change predicted to occur up to 2025, with increasing numbers of elderly in all countries. However, increasing uptake of treatment would on average reduce the increase in the number of fractures between 2010 and 2025 by 13%.

The pattern of increased annual number of fractures is apparent also when separated by type of fracture (Table 69). With the current treatment uptake hip fractures are expected to increase on average by 33% between 2010 and 2025 in EU5 and Sweden closely followed by "other" fractures, spine fractures and forearm fractures (30%, 28% and 22% respectively). Spain is expected to have the highest relative increase in number of fractures across all fracture types (35% for forearm fractures to 47% for hip fractures). However, if the

"target uptake" is reached the number of fractures will in 2025 in EU5 and Sweden be decreased by 4.8%, 5.2%, 2.3% and 2.0% at the hip, spine, forearm and "other", respectively, compared to the current treatment uptake. The effect of the increased uptake is greatest in Germany where hip, spine, forearm and "other" fractures are expected to decrease in 2025 by 6.9%, 7.5%, 3.1% and 2.8%, respectively.

The annual reduction in 2025 in the absolute number of fractures from increasing treatment uptake was estimated at 95,067 in EU5 and Sweden. In the individual countries the number ranged from 4,000 fractures in Spain up to 40,000 in Germany (Fig. 59). The accumulated number of potentially avoided fractures from 2010 through 2025 was estimated at 698,743.

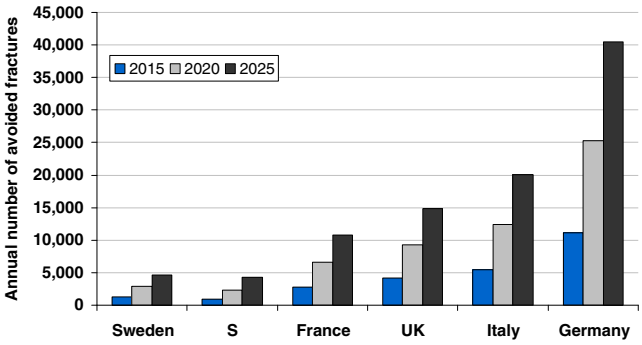
Table 68 Projected annual number of fractures up to 2025, with and without increasing treatment uptake

		2010	2015	2020	2025
Sweden	Current treatment uptake	106,976	113,566	121,920	132,406
	Approaching "target treatment uptake"	106,976	112,264	119,064	127,772
	Fractures avoided per year	-	1,302	2,856	4,634
UK	Current treatment uptake	534,583	573,633	616,866	662,121
	Approaching "target treatment uptake"	534,583	569,423	607,602	647,263
	Fractures avoided per year	-	4,211	9,264	14,857
France	Current treatment uptake	379,493	428,075	470,393	506,995
	Approaching "target treatment uptake"	379,493	425,246	463,741	496,238
	Fractures avoided per year	-	2,829	6,652	10,757
Germany	Current treatment uptake	734,208	804,955	880,371	936,055
	Approaching "target treatment uptake"	734,208	793,777	855,125	895,588
	Fractures avoided per year	-	11,178	25,246	40,468
Italy	Current treatment uptake	502,333	553,543	602,908	644,798
	Approaching "target treatment uptake"	502,333	548,124	590,553	624,703
	Fractures avoided per year	-	5,419	12,355	20,095
Spain	Current treatment uptake	202,779	232,360	261,628	290,140
	Approaching "target treatment uptake"	202,779	231,431	259,264	285,885
	Fractures avoided per year	-	929	2,364	4,255

Table 69 Projected annual number of fractures up to 2025 with and without increasing treatment uptake by site of fracture

		Hip		Spine		Forearm		Other	
		2010	2025	2010	2025	2010	2025	2010	2025
Sweden	Approaching "target treatment uptake"	20,292	24,273	16,439	19,181	16,389	18,815	53,856	65,239
	Current treatment uptake	20,292	25,759	16,439	20,491	16,389	19,353	53,856	66,804
	Fractures avoided per year	-	1,486	-	1,310	-	538	-	1,565
UK	Approaching "target treatment uptake"	79,492	95,689	65,783	78,493	66,710	79,129	322,598	393,952
	Current treatment uptake	79,492	99,382	65,783	81,682	66,710	80,708	322,598	400,348
	Fractures avoided per year	-	3,693	-	3,189	-	1,579	-	6,396
France	Approaching "target treatment uptake"	74,359	98,858	56,202	72,561	56,627	69,484	192,305	255,334
	Current treatment uptake	74,359	102,320	56,202	75,110	56,627	70,580	192,305	258,986
	Fractures avoided per year	-	3,462	-	2,548	-	1,095	-	3,652
Germany	Approaching "target treatment uptake"	132,715	164,023	115,394	132,520	119,713	138,625	366,386	460,421
	Current treatment uptake	132,715	176,119	115,394	143,233	119,713	143,055	366,386	473,648
	Fractures avoided per year	-	12,096	-	10,714	-	4,431	-	13,227
Italy	Approaching "target treatment uptake"	96,577	120,873	77,567	92,489	77,378	91,820	250,812	319,521
	Current treatment uptake	96,577	126,804	77,567	97,704	77,378	94,192	250,812	326,098
	Fractures avoided per year	-	5,931	-	5,215	-	2,372	-	6,577
Spain	Approaching "target treatment uptake"	40,235	57,790	29,361	41,240	29,451	39,265	103,731	147,590
	Current treatment uptake	40,235	59,215	29,361	42,182	29,451	39,652	103,731	149,091
	Fractures avoided per year	-	1,425	-	942	-	387	-	1,501

Fig. 67 Number of fractures potentially avoided annually in the EU5 and Sweden from an increased treatment uptake up to 2025



6.5.2 BMD measurements

Increasing the treatment uptake to the levels in Table 65 and Table 66 would together with changing demography be associated with an increased need for treatment monitoring and diagnostics with BMD measurement. The requirement for assessing and monitoring the treatment of osteoporosis has been estimated at 10.6 DXA units per million of the general population [33, 34]. The DXA unit requirement should however vary with the treatment penetration in each country. For example, 10.6 units per million capita would with Germany's current treatment provision correspond to 406 measurements per unit per year if the assumption of 0.5 BMD measurements/year of treatment is considered. The corresponding number in Spain would be 1,275 measurements per DXA unit per year. It was estimated that the suggested increase in treatment uptake and changes in demography would be associated with a 2.4-fold increase in the necessary number BMD scans in the EU5 (Table 70).

Table 70 BMD scans needed for assessing and monitoring osteoporosis per year per 1,000,000 population

	BMD scans currently needed /year / 1,000,000	BMD scans needed 2025/year / 1,000,000	Relative increase
Spain	13,516	19,321	1.4
Sweden	4,992	14,939	3.0
Germany	4,303	19,047	4.4
Italy	7,690	21,005	2.7
UK	7,229	15,744	2.2
France	10,361	20,274	2.0
EU5	8,085	19,054	2.4

However, should case finding increasingly be based on absolute fracture probability, as estimated by FRAX, it may be possible to reduce the need for BMD measurement in some patients. Adopting a case finding with FRAX would likely reduce the need for DXA units since at least 1%-4% of men and 19%-21% of women older than 50 years will be at sufficiently high risk to warrant treatment without information of BMD (Tables 24 and 25 in Chapter 3).

6.5.3 QALYs

The number of lost QALYs follows a similar pattern as for the number of fractures. The total number of QALYs lost will continue to increase even if the "target uptake" is reached. With the current treatment penetration the total number of QALYs lost was projected to increase from 0.85 million in 2010 to 1.0 million in 2025, corresponding to an increase of 20%. Increasing the treatment uptake would results in 33,455 QALYs gained in 2025. 20% of the increase in QALYs lost between 2010 and 2025 would be avoided if the treatment uptake target is reached.

The average QALYs lost (Table 71) per fracture (Table 68) was estimated at 0.24 in the EU5+. This should be compared to 0.35 QALYs gained per avoided fracture if the treatment uptake were to increase. This discrepancy arises because:

- The risk reduction from treatment is larger for the more severe hip and vertebral fractures (compared to wrist fractures and "other" fractures).
- The proportion of elderly, in whom the risk of hip fracture is very high, is projected to increase.
- There will be a "lag" in the benefit of reduced prevalence of hip and vertebral fractures, both of which are associated with long term quality of life loss [1]. A reduced fracture incidence will theoretically not fully translate into a reduced prevalence until all patients with a prevalent fracture (at the time of risk reduction) have died.

Table 71 Projected QALYs lost due to fractures up to 2025, with and without increasing treatment penetration

		2010	2015	2020	2025
Sweden	Current treatment penetration	38,655	39,995	42,187	45,156
	Approaching "ideal treatment penetration"	38,655	39,628	41,235	43,410
	QALYs gained per year	-	367	952	1,746
UK	Current treatment penetration	163,156	169,422	178,460	189,325
	Approaching "ideal treatment penetration"	163,156	168,420	175,867	184,606
	QALYs gained per year	-	1,002	2,592	4,719
France	Current treatment penetration	135,222	143,612	153,941	165,785

	Approaching "ideal treatment penetration"	135,222	142,852	151,845	161,906
	QALYs gained per year	-	760	2,096	3,879
Germany	Current treatment penetration	254,468	267,438	285,409	304,865
	Approaching "ideal treatment penetration"	254,468	264,472	277,551	290,500
	QALYs gained per year	-	2,965	7,858	14,366
Italy	Current treatment penetration	181,486	190,343	202,302	215,891
	Approaching "ideal treatment penetration"	181,486	188,887	198,382	208,626
	QALYs gained per year	-	1,456	3,921	7,265
Spain	Current treatment penetration	72,414	77,590	84,236	92,176
	Approaching "ideal treatment penetration"	72,414	77,332	83,482	90,695
	QALYs gained per year	-	258	754	1,480

6.5.4 Cost of fractures in the future

The cost of fractures in the EU5+ was estimated to increase from €30.7 billion in 2010 to €38.5 billion in 2025 (Table 72). The steepest increases were estimated for France and Spain where total fracture costs by 2025 were projected to increase by 31% and 29% respectively. A majority of the increase in fracture related costs was attributable to hip fractures and "other" fractures sustained in the elderly +65 (data not shown).

Table 72 Projected annual fracture burden (€ 000,000) up to 2025 assuming current uptake of treatment

	2010	2015	2020	2025
Sweden	1,418	1,487	1,584	1,716
UK	5,515	5,831	6,217	6,680
France	4,744	5,266	5,760	6,213
Germany	9,146	9,852	9,852	11,504
Italy	7,010	7,505	8,068	8,652
Spain	2,864	3,117	3,393	3,707
All	30,696	33,059	34,875	38,470

6.5.5 Cost consequences of increased treatment uptake

The cost consequences due to increased treatment uptake depend on the increase in number treated, and the expected change in the number of incident fractures and prevalent fractures. Fig. 68 shows how the cumulative cost consequences from increasing treatment uptake were estimated to be distributed among cost of treatment cost of incident factures and cost of prevalent hip fractures. The reduced cost of incident fractures (light blue line) is immediately responsive to a treatment dependent reduction in fracture rates whereas the cost offsets from a reduced number prevalent fractures will appear as a delayed effect from a reduced fracture incidence over time (black dotted line). Increasing treatment uptake in the UK and Sweden was estimated to reach cost-neutrality around 2017–2021 with a reduced total cost thereafter (red dotted line), which implies that treatment costs alone not should limit an increased treatment provision in these countries. It should be noted, however, that future costs were not discounted which favours long-term investments. The cost-saving result was caused by the very low prices of generic alendronate (Table 67) and relatively high fracture risks in these countries. In general, the size of the cost consequences (both positive and negative) were dependent on the countries' population size, level of risk, and the magnitude of the increase in prescription necessary to reach the "target treatment uptake".

By 2025 the EU5 would be required to have increased annual spending on pharmacological fracture prevention by approximately €1,900 million (Table 73) from the level of 2010. Such an investment would also be associated with cost offsets of €838 million from reduced acute fracture costs (first year after the fracture) and €268 million from reduced costs of long-term care related to hip fractures. Of the included countries Germany would have to increase treatment uptake the most. Corresponding estimates for Germany were increased annual treatment spending by €763 million and cost offsets from avoided incident and prevalent fractures of €412 million and €97 million, respectively. Cost offsets from fewer prevalent fractures would continue to grow beyond 2025 in the hypothetical scenario explored here.

Fig. 68 Annual difference in projected costs with target treatment uptake compared to current treatment uptake in EU5 and Sweden, by cost type

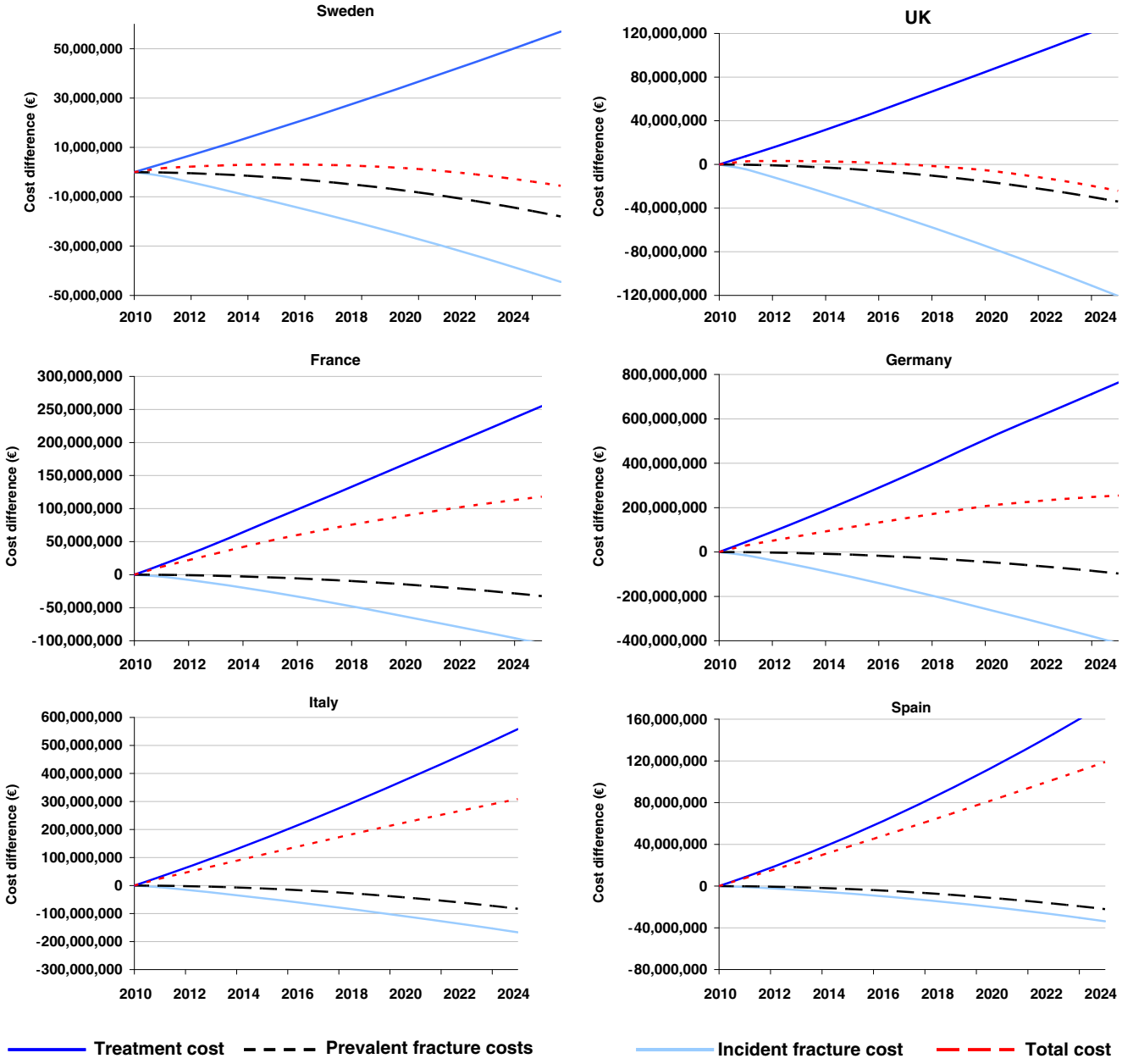


Table 73 Total accumulated cost consequences (EUR million) of reaching target treatment uptake by 2025

	Cost offsets due to incident fractures	prevalent fractures	Increased treatment cost
Germany	-412	-97	763
Italy	-167	-83	558
France	-105	-32	255
UK	-121	-34	130
Spain	-34	-22	175
Sweden	-45	-18	57
EU5	-838	-268	1,882
EU5+	-882	-286	1,939

Table 74 Macro level cost/QALY gained of reaching the target uptake by 2025 compared with keeping treatment provision on the current level

	Discounted[a] accumulated difference (M€)	Discounted[a] accumulated QALYs gained	Cost/QALY gained (€)
Sweden	12	8,362	1,494
UK	-46	22,715	Cost-saving
France	799	18,188	43,933
Germany	1,792	68,613	26,121
Italy	1,888	34,268	55,095
Spain	683	6,621	103,178

[a]An annual discount rate of 3% was used for all countries.

6.5.6 Cost-effectiveness on a macro level

Because of large differences between current treatment uptake as well as fracture risks, fracture prevalence and drug costs in different countries, the absolute results vary widely. Because Spain, for instance, already has both a relatively high prescription rate and a relatively low fracture risk, there is a *ceteris paribus* smaller gain per capita from closing the treatment gap. From the estimated burden estimations it is possible to calculate an incremental cost-effectiveness ratio on a macro level of increasing the treatment uptake towards the suggested target level (Table 74). The necessary investment in terms of treatment costs and associated cost offsets from avoided fractures up to 2025 were discounted to present value. The same was done with any future QALYs gained that arise due to increased treatment uptake.

Due to the low price of generic alendronate, and to a smaller extent to factors like fracture risk, fracture costs, and demography, increasing uptake over the 15-year period was estimated to be cost-saving in the UK. Macro cost-effectiveness of increasing treatment uptake in the other analysed countries ranged from €1,494/QALY in Sweden to 103,178 in Spain. Cost-effectiveness analyses of fracture prevention [19, 23, 25, 26] usually evaluate treatment in a carefully defined target population with a specific T-score, fracture prevalence, and age at start of treatment. The present analysis assumed a 80/20 mix of generic alendronate and branded treatment and that osteoporosis on average is associated a 2-fold risk of fracture compared with that of the general population. Notwithstanding the crude methods, the present analysis reaches results comparable to recent analyses [25, 28, 35] of the cost-effectiveness of fracture prevention in European perspective.

The treatment uptake future projections and macro cost-effectiveness analyses are somewhat crude but do still provide an indication of how to improve osteoporosis management in the countries analysed in this report. The poor treatment provision (Chapter 5), low drug costs, and higher fracture risks in Sweden, Germany, France and the UK suggest that treatment uptake could be increased cost-effectively, or even with cost-savings, in these jurisdictions.

Our results indicate that treatment uptake in Spain only may be increased marginally, and that the cost-effectiveness of doing so was estimated to be poor. The Prospective Observational Study Investigating Bone Loss Experience in Europe (POSSIBLE EU) is a longitudinal, non-interventional cohort study with the objective to examine the use of osteoporosis medications in EU5 [36]. The study (see Chapter 2) found that only 55% of Spanish patients had low BMD (<−2.5 SD), a prior fracture and/or glucocorticoid therapy, which implies that guideline adherence is not satisfactory. Furthermore, Spain has the lowest fracture risk of the analysed countries (Table 26) and taking steps towards price reductions of generic alendronate (Chapter 5) would thus be preferable to allow more patients to be cost-effectively treated.

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