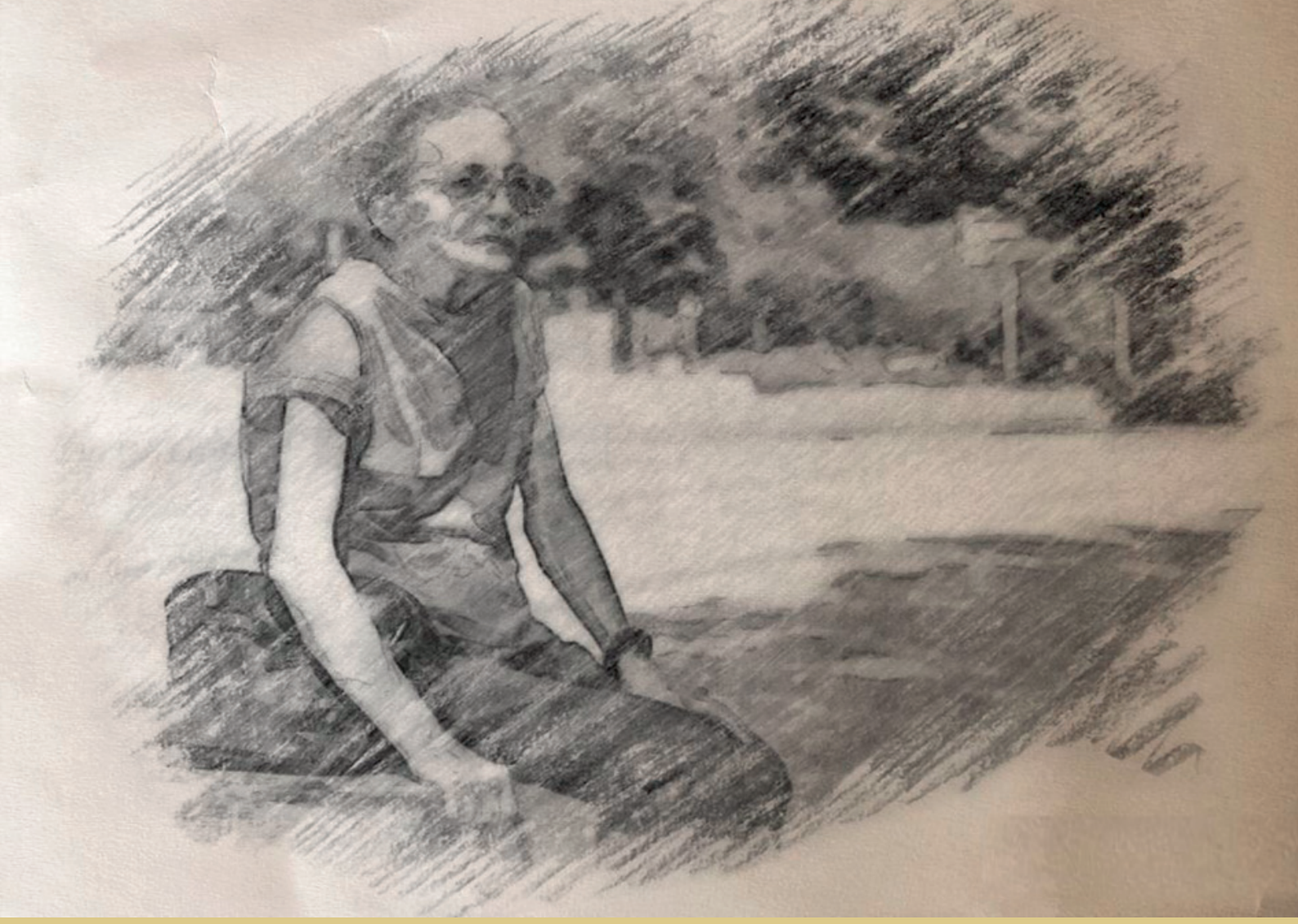

Andréa Ascenção Marques

FRAX® ADAPTATION AND VALIDATION FOR PORTUGUESE POPULATION (FRAX®-PORT) WITH SOCIO-ECONOMIC STUDY AND EVALUATION OF THE UTILITY OF THE INSTRUMENT TO THE PATIENT

Tese de doutoramento no Programa de doutoramento em Ciências da Saúde, no ramo Enfermagem, orientada pelos Professores Doutores José António Pereira da Silva, Aida Maria Cruz Mendes e Óscar Manuel Lourenço, apresentada à Faculdade de Medicina da Universidade de Coimbra.

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ANDRÉA ASCENÇÃO MARQUES

FRAX® ADAPTATION AND VALIDATION FOR PORTUGUESE POPULATION (FRAX®-PORT) WITH SOCIO-ECONOMIC STUDY AND EVALUATION OF THE UTILITY OF THE INSTRUMENT TO THE PATIENT

TESE DE DOUTORAMENTO EM CIÊNCIAS DA SAÚDE, RAMO ENFERMAGEM, APRESENTADA À FACULDADE DE MEDICINA NA UNIVERSIDADE DE COIMBRA

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ABSTRACT

This thesis presents the foundations and results of four years of work dedicated to changing the face of osteoporotic fracture prevention in Portugal, from the level of individual patient management to the overarching spheres of national health policies. This has been achieved through a systematic strategy to collect scientifically robust evidence regarding the national reality in this field, submitting it to rigorous analyses and, finally, transforming the results in algorithms and recommendations that are applicable to clinical practice and supported by broad consensus and endorsement by medical scientific societies.

Chapter 1 presents a general description of the individual and social problem represented by osteoporosis and osteoporotic fractures, referring its epidemiological features, socioeconomic impact, risk factors and prevention strategies that can be lead by nurses. The chapter ends with a description of the state of the fragility fracture epidemics and strategies dedicated to its prevention in Portugal before this work was started.

In Chapter 2 we present the results of a systematic literature review and meta-analyses which strongly supports the decision to select FRAX® as the most appropriate tool to predict fracture risk in the general Portuguese population, among the currently available.

In Chapter 3, we present the epidemiology of osteoporotic hip fractures in the Portuguese population, based on data collected from the National Hospital Discharge Register (5-year period). These data were then combined with National Statistics on resident population and mortality statistics, provided by the Portuguese Statistics Institute to support the development of the Portuguese FRAX® model (FRAX®-Port). FRAX®-Port was endorsed by a panel composed of representatives of all National relevant societies and independent experts.

Chapter 4, describes the results from a multicentre study (three prospective cohorts)

designed to evaluate the performance of FRAX® in predicting the 10-year probability of osteoporotic fractures in the general Portuguese population. We also investigated the added value of bone densitometry to the performance of FRAX®-Port. This work is remarkable for the large number of patients, more than 2500, and the duration of follow-up (>9 years).

In Chapter 5, we present an estimation of the burden represented by hip fractures in

Portugal, in terms of overall societal costs, the per-patient costs and deleterious effects upon health-related quality of life. We used real-life individual patient data, collected from persons selected in a stratified random fashion designed to represent the distribution of hip fractures in the Portuguese population.

Chapter 6 is dedicated to the establishment of risk-based thresholds for pharmacological intervention in osteoporosis. Based on data from the previous chapter, we established the

FRAX®-based 10-year probabilities of major and hip fractures (with and without Bone Mineral Density) above which pharmacologic interventions become cost effective in the Portuguese social and economic context. For this purpose we used a previously developed and internationally validated state transition Markov model. Cost-effective intervention thresholds for four different treatment drugs were established.

Chapter 7 conveys the multidisciplinary Portuguese recommendations on dual energy X-ray absorptiometry (DXA) request and indication to initiate medication aimed to the prevention of fragility fractures. This was developed on the basis of the results described previously and submitted to the consensus review and approval by multidisciplinary panel, representing the full spectrum of medical specialties and patient associations devoted to osteoporosis, as well as national experts in this field and in health economics. This document was adopted as the basis of the Portuguese Society of Rheumatology recommendations for the prevention and treatment of Osteoporosis and also for the National authoritative "Norma de Orientação Clínica" in this field, both in preparation.

In Chapter 8, we present a project aimed at fostering the general public awareness and involvement in the efforts to restrain the ever-growing burden of osteoporosis, using an approach based on patient centered care and e-Health. To this purpose, a web platform will be created, which allows lay members of the general population to calculate the subsequent 10-years' probability of osteoporotic fracture (using FRAX®-Port) for themselves or relatives. On this basis, advice will be provided on actions to take, from life style changes to consulting a physician or other health professional. The platform will also provide a wealth of information regarding osteoporosis causes, consequences and prevention strategies.

In Chapter 9, we present a proposal for the creation of a fracture liaison services in CHUC and in Portuguese Hospitals as a crucial instrument to guarantee that all patients with a fracture receive appropriate treatment and education to prevent subsequent ones. This opportunity for an effective intervention is frequently lost in most countries, including Portugal, as shown by our own results.

The work present in this thesis is an original and unique opportunity to change the field and curtail the epidemics of osteoporotic fractures in our country. It will, hopefully, contribute significantly to the success of the strategy proposed and the attainment of the invaluable health benefits it holds for our population.

RESUMO

Esta tese apresenta as bases e os resultados de quatro anos de trabalho que contribuíram para a mudança na prevenção das fraturas osteoporóticas em Portugal, desde a gestão individual do doente até às políticas nacionais de saúde. Foi utilizada uma estratégia sistemática de colheita de evidência cientificamente robusta sobre a realidade nacional neste campo, submetendo-a a rigorosas análises e, finalmente, transformando os resultados em algoritmos e recomendações que são aplicáveis à prática clínica e apoiados e endossados por amplo consenso por um conjunto de sociedades científicas médicas.

O Capítulo 1 explicita uma descrição geral do problema individual e social da osteoporose e das fraturas osteoporóticas, abordando características epidemiológicas, impacto socioeconómico, fatores de risco e estratégias de prevenção que podem ser lideradas pelos enfermeiros. Terminámos com uma descrição do estado epidemiológico das fraturas de fragilidade e das estratégias dedicadas à sua prevenção em Portugal antes do início deste trabalho.

No Capítulo 2 apresentamos os resultados de uma revisão sistemática da literatura e metanálise que sustentam fortemente a decisão de escolher o FRAX® como a ferramenta mais adequada para predizer o risco de fratura na população geral Portuguesa, dentro das atualmente disponíveis.

No Capítulo 3, apresentamos a epidemiologia das fraturas osteoporóticas do anca na população portuguesa, com base nos dados recolhidos no Registo Nacional de altas Hospitalares (período de 5 anos). Estes dados foram combinados com as estatísticas nacionais de população residente e mortalidade, fornecidas pelo Instituto Nacional de Estatística para apoiar o desenvolvimento do modelo Português do FRAX® (FRAX®-Port). O FRAX®-Port foi aprovado por um painel composto por representantes de todas as sociedades nacionais relevantes no domínio da osteoporose e peritos independentes.

O Capítulo 4 descreve os resultados de um estudo multicêntrico (três coortes prospectivas) concebido para avaliar o desempenho do FRAX® na previsão da probabilidade a 10 anos de fracturas osteoporóticas na população geral Portuguesa. Também investigamos o potencial de adicionar a densitometria óssea ao FRAX®-Port. Este trabalho é notável pelo grande número de doentes, mais de 2500, e a sua duração do seguimento (> 9 anos).

No Capítulo 5, apresentamos uma estimativa do encargo das fraturas da anca em Portugal, em termos de custos sociais, custos por doente e os efeitos deletérios sobre a qualidade de vida relacionada com a saúde. Utilizou-se para isso dados reias de doentes individuais, colhidos de pessoas selecionadas de forma aleatória, estratificados para representar a distribuição de fraturas da anca na população Portuguesa.

O Capítulo 6 é dedicado ao estabelecimento dos limiares de risco para intervenção farmacológica na osteoporose. Com base nos dados do capítulo anterior, estabelecemos a probabilidade de fracturas major e da anca (com e sem densidade mineral óssea) a 10 anos baseadas no FRAX® acima dos quais intervenções farmacológicas se tornam rentáveis no contexto social e económico Português. Para isso, utilizou-se um modelo de Markov de previamente desenvolvido e validado internacionalmente. Foram estabelecidos limiares de intervenção de custo-benefício para quatro fármacos diferentes.

O Capítulo 7 apresenta as recomendações multidisciplinares Portuguesas para o pedido de densitometria (DEXA) e a indicação para iniciar terapêutica destinada à prevenção de fraturas de fragilidade. Este foi desenvolvido com base nos resultados descritos anteriormente e submetido à revisão consensual e aprovação por um painel multidisciplinar, representando todo o espectro de especialidades e associações de doentes dedicadas à osteoporose, bem como especialistas nacionais neste campo e em economia da saúde. Este documento foi adoptado como base das recomendações da Sociedade Portuguesa de Reumatologia para a prevenção e tratamento da Osteoporose e também para a "Norma de Orientação Clínica" nacional neste domínio, ambos em preparação.

No Capítulo 8, apresentamos um projeto destinado a promover a conscientização e o envolvimento do público em geral nos esforços para conter o problema cada vez maior da osteoporose utilizando para isso uma abordagem centrada no doente e nas tecnologias da saúde. Para isso, será criada uma plataforma web, que permitirá aos membros leigos da população geral calcular a probabilidade subsequente a 10 anos de fratura osteoporótica (usando FRAX®-Port) para si ou para os seus familiares. Será fornecido aconselhamento sobre o que fazer, mudanças de estilo de vida, quando consultar um médico ou outro profissional de saúde. A plataforma também irá fornecer informações sobre as causas da osteoporose, consequências e estratégias de prevenção.

No Capítulo 9, apresentamos uma proposta para a criação de um serviço de ligação de fraturas no CHUC e nos Hospitais Portugueses como um instrumento crucial para garantir que todos os doentes com fratura recebam tratamento e educação adequados para evitar fraturas subsequentes. Esta oportunidade para uma intervenção eficaz é frequentemente perdida na maioria dos países, incluindo Portugal, como demonstrado pelos nossos próprios resultados.

O trabalho apresentado nesta tese é uma ferramenta original e única para reduzir a epidemia das fraturas osteoporóticas no nosso país. Espera-se que contribua significativamente para o sucesso da estratégia proposta e para a obtenção dos inestimáveis benefícios para a saúde que ela tem para a nossa população.

THESIS STRUCTURE

This thesis is written in the first person plural to acknowledge the contribution of supervisors and co-authors. However, I have been responsible for running the entire projects including data collection and analyses, and writing of papers and thesis. I am confidently co-responsible for all aspects of the research described here, from project design to final publications.

The present thesis is divided into 10 chapters, with 6 of them (chapters 2 to 7) corresponding to papers already published, addressing research questions within the scope of this thesis.

In **Chapter 1** we present a general introduction to the problem of osteoporosis and osteoporotic fractures, referring its epidemiological features, socio-economic impact, risk factors and prevention strategies. It also covers the specific contribution that nurses may play in screening, education for prevention, management, and education after diagnosis. This chapter ends with the aims of this thesis.

In **Chapter 2** we present the results of a systematic literature review and meta-analyses with the aim of describing all relevant evidence on the structure and performance of the currently available tools to predict fracture risk in the general population.

In **Chapter 3,** through data collected from the National Hospital Discharge Register (5-year period) combined with National Statistics on the Portuguese population and mortality statistics, provided by the Portuguese Statistics Institute, we present the epidemiology of osteoporotic hip fractures in the Portuguese population. These data were then used to support the development of the Portuguese FRAX® model (FRAX®-Port), a project that involved a multidisciplinary panel of experts. We discuss the underlying assumptions and limitations of this model and present the process that allowed its nation-wide endorsement.

In **Chapter 4**, we describe the results of a multicentre study (three prospective cohorts) designed to evaluate the performance of the Portuguese version of FRAX® in predicting the 10-year probability of osteoporotic fractures in the general population in Portugal. We also investigated the added value of bone densitometry to the performance of FRAX®.

In **Chapter 5**, we present an estimation of the burden represented by hip fractures in Portugal, in terms of overall societal costs, the per-patient costs and deleterious effects upon heath related quality of life. We used real-life individual patient data, collected from patients randomly selected to represent the distribution of hip fractures in the Portuguese population.

In **Chapter 6**, we present the work that, based on data from the previous chapter, allowed the establishment of the FRAX®-based ten-year probabilities of major and hip fractures (with and without BMD) above which pharmacologic interventions become cost effective in the

Portuguese context. For this purpose we used a previously developed and internationally validated state transition Markov model. Cost-effective intervention thresholds for 4 different treatment drugs were established.

Chapter 7 conveys the multidisciplinary Portuguese recommendations on dual energy X-ray absorptiometry (DXA) request and indication to initiate medication aimed to the prevention of fragility fractures. This was developed on the basis of the results described previously and submitted to the consensus review and approval by multidisciplinary panel, representing the full spectrum of medical specialties and patient associations devoted to osteoporosis, as well as national experts in this field and in health economics.

In **Chapter 8**, we present a project aimed at fostering the general public awareness and involvement in the efforts to restrain the ever-growing burden of osteoporosis. To this purpose, a web platform will be created, which allows lay members of the general population to calculate the subsequent 10 years' probability of osteoporotic fracture (using FRAX®-Port) for themselves or relatives. On this basis, advice will be provided on actions to take, from life style changes to consulting a physician or other health professional. The platform will also provide a wealth of information regarding osteoporosis causes, consequences and prevention strategies.

In **Chapter 9**, we describe the project for the creation of a fracture liaison service in Portuguese Hospitals and in Centro Hospitalar e Universitário de Coimbra. A liaison service is designed to care all patients that suffered an osteoporotic fracture and ensure that all receive adequate treatment, thus targeting a well-known and serious problem all over the world. These services are usually managed by a specialist nurse, who provides complementary information to the patient and family and acts as a liaison element between different health professionals (orthopaedist, general practitioner, community nurses, rheumatologist, and others).

Chapter 10 is dedicated to the combined discussion of all studies, considering the strengths and limitations of the research findings, their potential implications in an integrated perspective, while identifying potential areas for further work.

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Chapter 1

BACKGROUND

BACKGROUND

Definition of osteoporosis

Despite being a disease already present in 4,000-year-old Egyptian mummies and depicted in old women in Renaissance paintings,[1] the word "osteoporosis" was used for the first time by the French surgeon and pathologist Jean Lobstein (1777–1835) to describe the porous bones he observed in autopsies.[1] The concept of osteoporosis was introduced in 1824 by the English surgeon Sir Astley Cooper (1768-1841), who noted a relation between reduced bone mass and hip fractures in elderly.[2] The first article with the word osteoporosis available in PubMed dates to late 1889 in a publication entitled “Osteoporosis of the Cranial Vault”.[3] A few decades later, in the 1930s, osteoporosis became an object of clinical interest due to the American endocrinologist Fuller Albright (1900-1967), who described it as a consequence of menopause, thus boosting the study of the metabolic origins of this condition.[4] In the last decades of the twentieth century, osteoporosis became widely recognized as a major public health issue by both health professionals and the general public. However, an official definition of osteoporosis was only established in 1991, when a consensus group defined it as a “systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk”.[5] In 2001, the National Institute of Health (NIH) updated the definition of osteoporosis to “a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk fracture; bone strength reflects the integration of two main features: bone density and bone quality”.[6]

In the year 1992, the World Health Organization (WHO), having recognized osteoporosis as an established and well-defined disease,[7] established a consensus group to evaluate the available methods for fracture risk assessment and their suitability for use in screening of osteoporosis, as a means to support effective preventive and therapeutic interventions. As a result, diagnostic criteria for osteoporosis were published in 1994,[7] based on the measurement of bone mineral density (BMD), which are still generally accepted. This definition is based on BMD, recognizing the strong inverse relationship between bone mineral density and fracture risk (see below).[7]

A BMD T-score ≤−2.5, measured by dual energy X-ray absorptiometry (DXA), was the cut-off chosen to define osteoporosis, because “*a measured value of bone mineral density more than 2.5 standard deviations bellow the mean for young healthy adult women (T-score) at any site (spine, hip or mid-radius) identifies 30% of all postmenopausal women as having osteoporosis*” (p.14).[7] The WHO criteria for different definitions relevant to osteoporosis are shown in Table 1.

Table 1. WHO criteria for diagnosis of osteoporosis

BMD T-score	Diagnosis
≥ -1	Normal
-1 to -2.5	Low bone mass
≤ -2.5	Osteoporosis
≤ -2.5 with existing fracture	Severe osteoporosis

This definition stood the proof of time and is still consensually regarded as valid, despite the remarkable progress in the field of osteoporosis over these 22 years. It has provided a valuable service in clearly defining the condition, an indispensable pre-requisite for productive research, both for bench and bedside.

Bone Mineral Density

Bone is a biologically active tissue that undergoes continuous renovation under the effects of specialized cells in bone formation, osteoblasts, and others in bone resorption, osteoclasts, which work in strict coordination. Bone matrix is essentially composed of type I collagen and calcium salts, mainly hydroxyapatite. DXA measures de amount of calcium per unit of area, (as this is a two-dimensional imaging technique). During the first decades of life, bone formation is predominant: bones increase in size and in mineral content. BMD reaching a peak between 20 and 30 years of age. In the absence of deleterious conditions, BMD is relatively stable until the menopause in women and around 50 years of age in men. From then onwards, due to the lack of estrogens and many other factors related to ageing, bone resorption becomes more intense than formation: BMD decreases progressively, bone becomes more fragile and may suffer fracture upon low intensity trauma, before or after reaching densitometric criteria for osteoporosis. In females, this process is accelerated by a period of rapid bone loss that follows the menopause. Peak bone mass, which is essentially dependent on genetic background and healthy lifestyle in childhood and adolescence, is major determinant of BMD later in life.

Figure 1 represents the change in bone mineral density for women and men during lifetime.

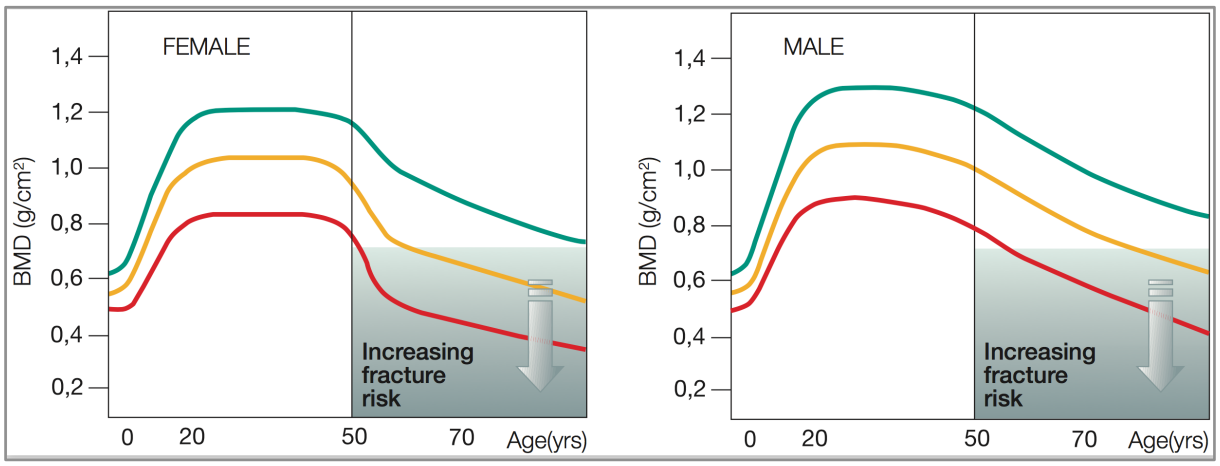

Figure 1. Change in bone mass for women and men during lifetime.

Reproduced from da Silva, JAP. Reumatologia Prática. (2.nd ed.) Coimbra: Diagnósteo, 2005.[8]

BMD is described, for diagnosis and risk estimates, in terms of T scores, i.e. the number of standard deviations that separate the BMD of the individual from the average BMD of healthy young adults of the same gender and race (peak bone mass). This indirect measure was established to account for the systematic difference observed in absolute BMD values when measured with different instruments – T-scores remain relatively comparable between different densitometry equipment's, despite differences in absolute values.

The relationship between T scores and risk of fracture is quite strong. It has been shown, based on large scale epidemiological data that, at the age of 65 years, the risk for hip fractures increases by ~2.94 fold in men and by 2.88 fold in women for each SD decrease in femoral neck BMD. Regarding osteoporotic fractures as a whole, per each SD decrease in femoral neck BMD, at the age of 65 years, the risk of osteoporotic fractures increased by 1.41 in men and 1.38 in women.[9]

This relative risk relationship provides the foundations for the WHO criteria for osteoporosis. However, it must be kept in mind that this is an operational diagnosis: several other conditions, other than osteoporosis, may reduce BMD, such as osteomalacia, tumor infiltration (eg multiple myeloma) or renal osteodystrophy. However, because osteoporosis is far more prevalent that these other conditions, the diagnosis based on BMD was accepted for large-scale diagnosis, as opposed to the bone biopsy that would be required for formal pathological diagnosis. [10 11]

Definition of osteoporotic fracture

Fractures, and their sequelae, are the most important consequences of osteoporosis,

constituting the main factor for the remarkable socio-economic impact of this condition.[i]

For epidemiological purposes, fractures are designated as osteoporotic when they occur after the age of 50 years and result from mechanical forces that would not ordinarily result in fracture (low-level trauma).[12 13] These are also described as "fragility fractures". Trauma is considered "low level" when its intensity is equivalent to that of a fall from standing height or less.[14] The designation of osteoporotic or fragility fracture additionally requires that it is not a consequence of other pathological causes, such as bone metastasis or primary tumors[14].

The vast majority of hip, forearm, vertebral or humeral fractures occurring after 50 years of age is consequence of low energy injuries and is generally considered osteoporotic fractures.[15 16] Fractures occurring in other sites, ribs, tibia, pelvis, are more difficult to define as osteoporotic.[17] The possibility that fractures are not solely due to osteoporosis may justify more detailed investigation in the individual patient, but osteoporosis may always be a contributing factor, especially after the age of 50 years, given that all bones are weakened by this condition.[18]

These latter considerations also apply to arguments regarding the intensity of trauma causing fracture. Although high intensity trauma precludes classification as osteoporotic fracture, it is intuitive that patients with osteoporosis will suffer a greater number of fractures than normal, at a similar intensity of trauma.[14 19] This, together with the fact that the vast majority of fractures over the age of 50 are due to osteoporosis, justifies that in large epidemiological studies all fractures occurring after this age-limit are accounted for as osteoporotic.[14]

Epidemiology of osteoporotic fractures: Incidence and future projections

In 1997 the National Osteoporosis Foundation (USA) projected that there were more than 75 million people with osteoporosis in the United States, Europe and Japan.[20]

Johnell and Kanis[21] estimated that in the year 2000, osteoporosis caused more than 9 million fractures worldwide every year (1.6 million at the hip, 1.7 million at the forearm and 1.4 million vertebral). Of these around 3.1 million occurred in Europe.[21]

In 2010 the scenario had aggravated, as expected. Estimates indicated a total of about 27.6 million people aged 50–84 years with osteoporosis, only in the European Union, corresponding to approximately 6% of men and 21% of women of overall population within this age range.[22]

[i] The only reason why osteoporosis might deserve attention, if it weren't for factures, is the occasional patient whose osteoporosis works as an alert for a significant underlying disease (e.g.: hyperparathyroidism or multiple myeloma).

Osteoporotic fracture rates vary markedly between and within countries. The reasons are not completely known, but are partly associated with economic prosperity and longevity of populations.[23] Scandinavia, North-Western Europe and North America have the highest incidence of hip fractures among developed countries

Osteoporosis, is already a momentous public health issue,[24] and its impact will tend to increase with the progressive aging of populations worldwide.[18] [17] In fact, there is an exponential increase of risk of fractures with age, after the age of 50 (Figure 2).

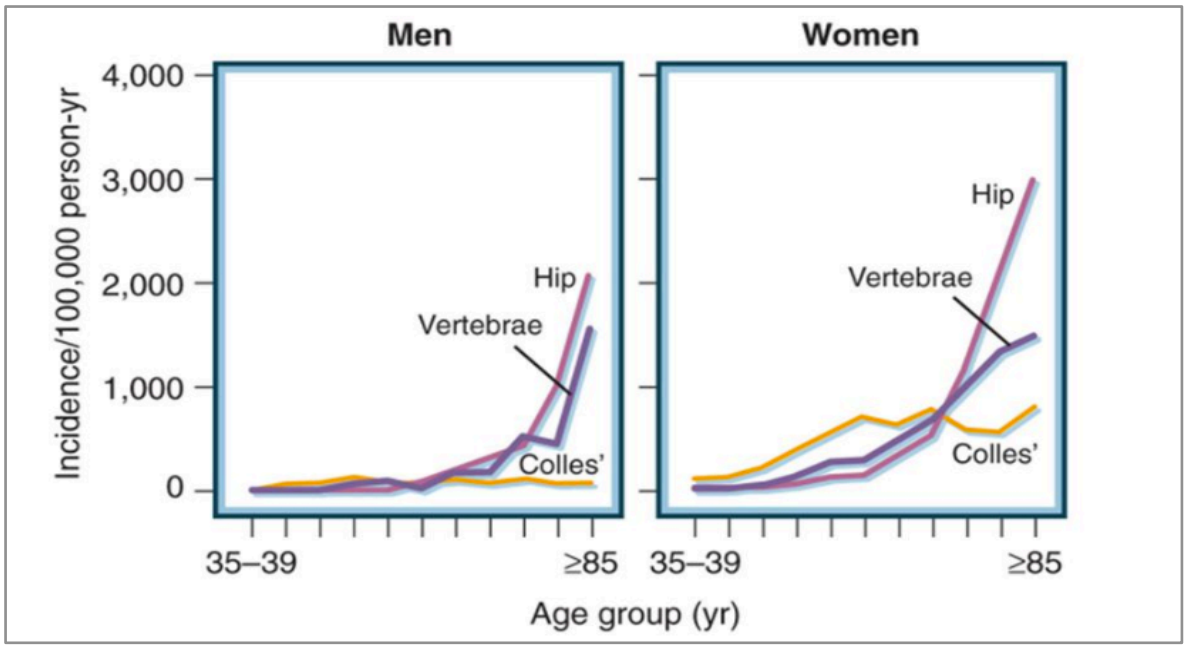

Figure 2. Age-specific and sex-specific incidence of clinical vertebral, hip, and distal forearm fractures. Data derived from Felsenberg D, Silman AJ, Lunt M, et al. Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS). Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 2002;17(4):716-24.[23] and from van Staa TP, Dennison EM, Leufkens HG, et al. Epidemiology of fractures in England and Wales. Bone 2001;29(6):517-22.[25] [26] and reproduced from Sambrook P, Cooper C. Osteoporosis. Lancet 2006;367(9527):2010-8.[17]

The strong relationship between age and osteoporotic fractures is the main explanation for the alarming projections of future incidence of osteoporotic fractures worldwide, shown in Figure 3 for hip.[27]

More recently, an Official European Union report on data from 2010 states that over 3.5 million new fragility fractures occurred every year in Europe alone (610,000 at the hip, 520,000 vertebral, 560,000 at the forearm and 1,800,000 at other sites) and that this number will rise to 4.5 million in 2025, corresponding to an increase of 28%.[28]

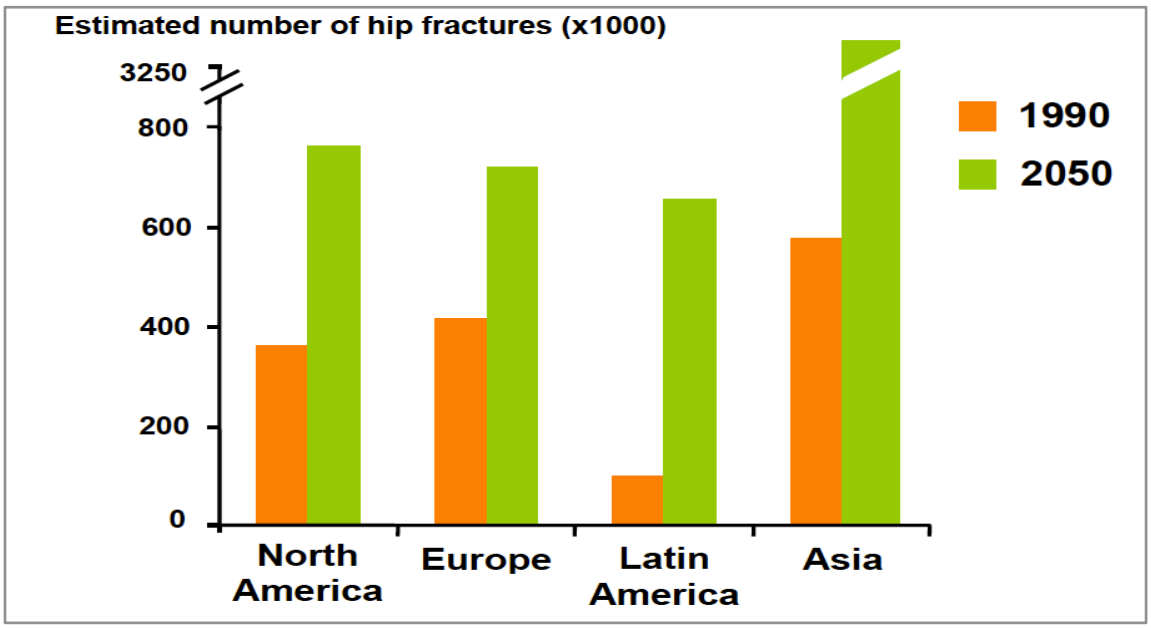

Figure 3. Projections of osteoporotic hip fractures incidence worldwide.

Reproduced from Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. Osteoporos Int 1992;2(6):285-9.[27]

Epidemiology of osteoporotic fractures: Socio-economic impact

Epidemiological studies are easier to perform and more reliable for hip fractures than for other skeletal locations, because, contrary to other fractures, hip fractures require hospitalization thus originating formal and traceable medical registries.[28] Other osteoporotic fractures are either frequently asymptomatic (e.g., vertebral fractures) or treated in emergency rooms and outpatients, seldom being the object of reliable registries. In fact, in most countries, calculations related to non-hip osteoporotic fractures are only estimates extrapolated from ratios observed in rigorously managed registries, especially from Sweden.[29 30] Overall, the quality and volume of epidemiological information available is much higher for hip than for other types of osteoporotic fractures.

Mortality and morbidity rates after an osteoporotic fracture vary according to age and site of fracture.[31 32 33] Hip fractures have the higher rates of mortality.[34] In women, approximately 50% of fracture-related deaths can be attributable to hip fractures, 28% to clinical vertebral and 22% to other fractures.[28] An estimated 740,000 deaths per year are associated with hip fractures worldwide.[35] Mortality associated with hip fracture increases with age and is higher in men than women.[35 36] In the UK, the 12-month survival rate after hip fracture for men is 63.3% (versus 90.0% expected in the age-matched population) and 74.9% for women (versus 91.1% expected).[26]

Regarding morbidity, osteoporotic hip fractures can be devastating due to debilitating psychological and physical sequelae.[31] Major lifestyle changes are imposed upon patients as

many become unable to perform daily living activities independently, such as bathing and toileting,[34] and over half of patients lose the ability to walk without assistance.[34] Fifteen to 25% of hip fracture victims require admission to long-term institutional care.[37] It is estimated that only 50% of these patients regain their pre-fracture functional status as judged by the ability to walk and the need for aids at home.[38]

The major clinical consequences of vertebral fracture are back pain, kyphosis, and height loss.[39] Severe kyphosis may reduce chest expansion, thus intensifying cardio-respiratory conditions and favoring infections, and increase abdominal pressure, leading to aggravated constipation and urinary incontinence. This context negatively impacts on quality of life and frequently leads to psychological disturbances such as depression and social isolation.[40] Distal radial fractures also lead to acute pain and loss of function, but functional recovery is usually good or excellent and they are not associated with excess mortality.[41]

In Europe, osteoporotic fractures were reported as accounting for more disability-adjusted-life-years (DALYs) lost in 2002 than common cancers, with the exception of lung cancer, and more than diseases such as hypertension, migraine and asthma (Figure 4).[21] Compared to other chronic musculoskeletal disorders, the overall impact due to osteoporosis was less than osteoarthritis but greater than rheumatoid arthritis.

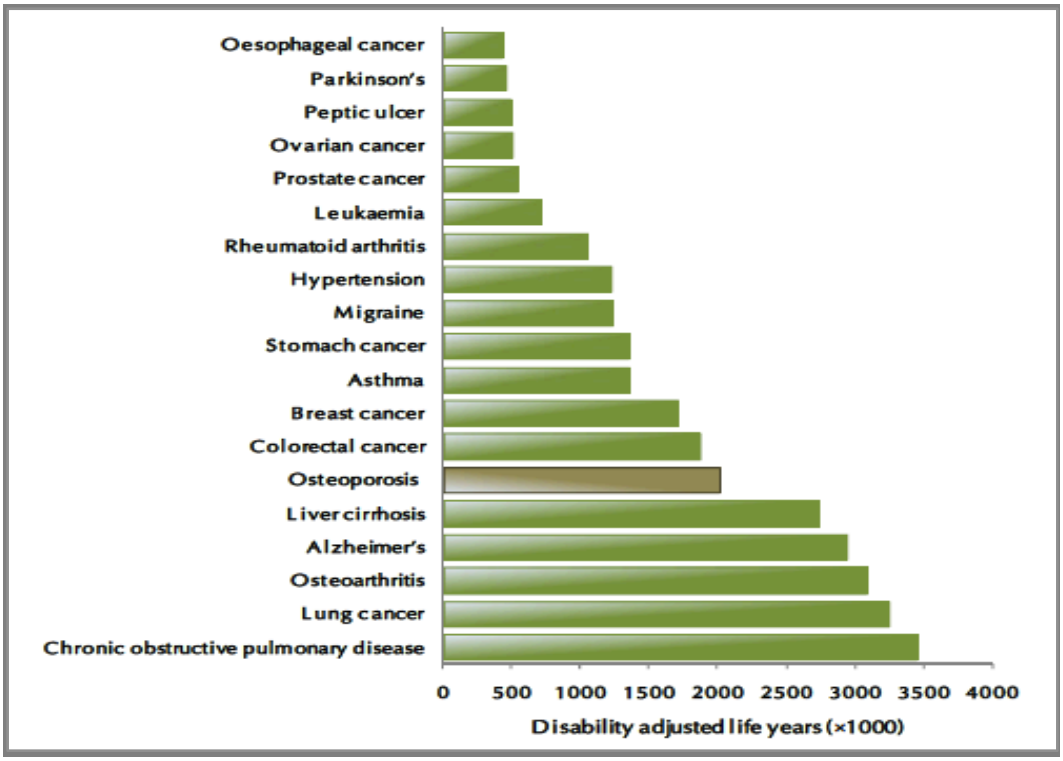

Figure 4. The estimated burden of chronic non-communicable diseases in Europe in 2002.

Reproduced from Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17(12):1726-33.[21]

Also important is the financial burden imposed by osteoporotic fractures upon societies and families. This includes direct medical costs (inpatient care, rehabilitation care, outpatient consultations, osteoporosis preventive medications, diagnostic tests and nursing care) and direct non-medical costs (long-term care, nursing home, patient's transportation, technical aids, home adaptations, home care, informal care and burial).[42] Estimates produced by Johnell and Kanis indicate that osteoporotic fractures account for circa 0.83% of the burden of non-communicable disease worldwide and 1.75% in Europe.[21] In the year 2000, the projected annual cost of osteoporotic fractures in the European Union was estimated at EUR 32 thousand million (only considering direct costs),[43] that was more than the annual cost attributed to type 2 diabetes.[44] Direct costs are expected to increase to EUR 76.7 billion by 2050.[21]

A recent Danish study estimated the total cost (medical, non-medical, informal care and indirect costs) of osteoporotic fractures in Denmark to EUR 1.5 thousand million in 2011.[45] In Austria, this total annual financial burden amounted to approximately EUR 685 million, the largest fraction of which was due to the informal care (30%), followed by costs for hospitalization (27%).[46] In Sweden annual fracture cost was estimated to be about 3.2% of the total health care costs.[47]

It is important to keep in mind that these are only estimates, naturally associated with a rather large margin of error and are very likely to be under-estimated. In fact, the exact costs of osteoporosis and osteoporotic fractures are very hard to determine for a number of reasons:[42 48]

- Costs vary considerably,
    - from region to region
    - according to the age of the patient
    - depending on site and severity of fracture
    - according to type and quality of outpatient care
- Other non-medical costs, such as transportation and supplementation are difficult to account for;
- Detail and reliability of national registers of fracture incidence and mortality, especially non-hip fractures, are limited;
- Evaluation of the impact on quality of life requires dedicated and logistically requiring studies.

Epidemiology of osteoporotic fractures: risk factors

The main risk factors for osteoporotic fractures are described in **Table 2**.[49] Their impact is briefly described in the text below.

Table 2. Non-modifiable and modifiable risk factors for osteoporotic fractures

Non-modifiable risk factors	Modifiable risk factors
Low Bone Mineral density[9 50]	Low Bone Mineral density[9 50]
Age[23]	Body mass index[51]
Gender (women)[23 52]	Smoking[53]
Ethnicity (Caucasian)[23 54 55]	Excessive alcohol intake[56]
Parent hip fractures[57]	Sedentary lifestyle[58-60]
Secondary causes of osteoporosis [52]	Falls [61]
Rheumatoid arthritis[52 62]	Low intake of calcium[63]
Chronic corticosteroid therapy[64 65]	Vitamin D deficiency[66 67]
Previous osteoporotic fractures[57 68]	

Low bone mineral density. Low BMD (measured with DXA) is one of the most important risk factors for fragility fractures[50]. It is considered both non-modifiable and modifiable since it is determined by a wide range of factors, including genes, age, gender and lifestyle factors, which differ in their accessibility to change.[69]

Bone mineral density is also pivotal because it mediates a substantial part of the impact of the factors described below[70]. However, in very single case, the following factors have been shown to influence the risk of fracture independently of BMD.[53 57 64 71 72]

Age. The frequency of fractures, especially at the hip, increases exponentially with age, especially after the age of 70, in both men and women, in most regions of the world.[23] The pattern of incidence of fractures over the age range varies according to the site considered (Figure 2). Forearm fractures show an increase in incidence in white women between the ages of 45 and 60 years (the earliest site having an increase with age), followed by a plateau. On the contrary, hip fractures steadily increase with age. This has been attributed to deteriorated neuromuscular reflexes with aging: younger patients tend to protect the fall with their hands, suffering wrist fractures, while older ones tend to fall sideways or backward. The incidence curve of vertebral fractures presents a slowing of the increase in the older ages, contrary to hip. This may be explained by the fact that vertebral fractures are frequently asymptomatic, and only about one-third of these patients come to medical attention and have radiographic confirmation of such fractures.[25]

BMD reaches a peak by the third decade of life and to decreases progressively after the

5th decade until the end of life, in both men and women (Figure 1).[73] The increase in fracture risk associated with age is, however, much more intense than could be explained by BMD alone. Other changes affecting the mechanical resistance of bone and the age-related increase in falls are considered responsible for this BMD-independent effect of ageing.[17]

Gender. Being female, especially over the age of 50[49] is a risk factor for fracture and this is essentially due a lower bone density throughout life, but also to the smaller section and cortical thickness of female bones.[19] In addition, women live longer than men, on average, which adds to the proportion of around 3 females to 1 male among the victims of fragility fractures.[23]

Ethnicity (Caucasian). Substantial differences have been shown in fracture incidence rates across different ethnic groups.[23] In the United States, the remaining lifetime risk of hip fracture at age 50 years is 15.8% and 6.0% in Caucasian women and men, respectively, compared to 2.4% and 1.9% in Chinese women and men, and 8.5% and 3.8% in Hispanic women and men.[74] Similar ethnic and race variability in women is observed for all fractures, with annualized rates greater than 2% for white and Native American women and lower rates for African American, Hispanic, and Asian women (Fig. 5).

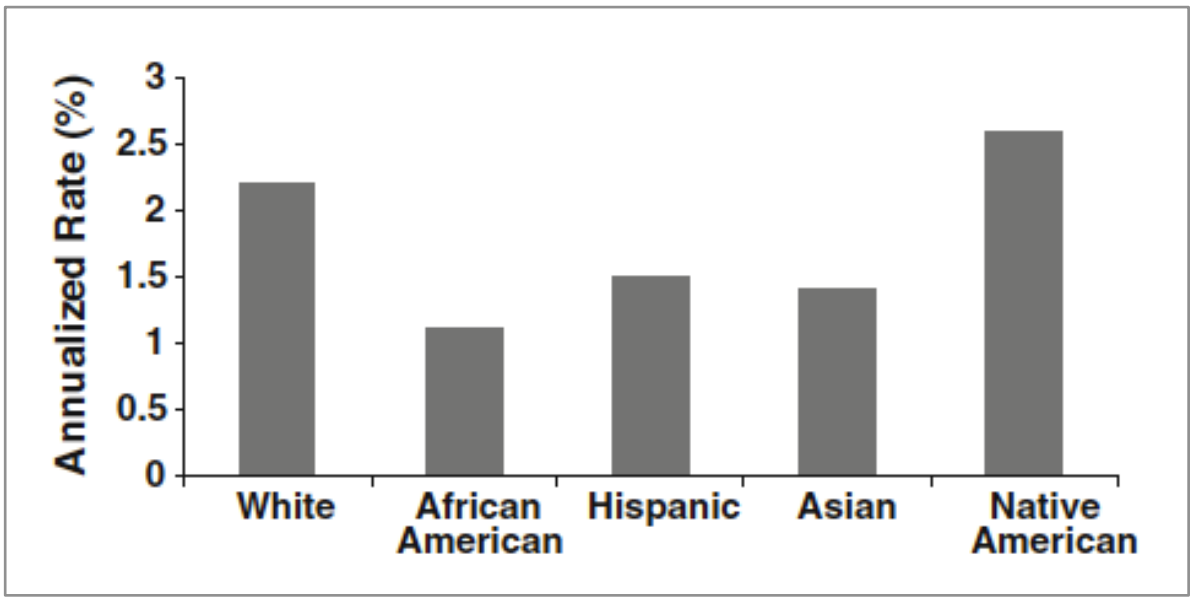

Figure 5. The graph shows annualized rates of fracture by race/ethnicity according to the Women's Health Initiative Observational Study. Derived from Cauley JA, Wu L, Wampler NS, et al. Clinical risk factors for fractures in multi-ethnic women: the Women's Health Initiative. J. Bone Min Res 2007;22(11):1816-26.[55] as reproduced from Cauley JA. Defining ethnic and racial differences in osteoporosis and fragility fractures. Clin Orthop Relat Res 2011;469(7):1891-9.[54]

Parent hip fractures. A history of fragility hip fracture in one of the parents is associated with significantly increased risk of any osteoporotic fracture in men and women, and this is largely independent from BMD value.[57]

Secondary causes of osteoporosis. There are a number of clinical disorders that affect

bone density and risk of fractures.[75] This diverse group includes type I diabetes (insulin treated), *osteogenesis imperfecta* in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease[52]. The true incidence of secondary causes of osteoporosis is controversial but several studies have estimated that it may be relevant in 20% to 30% of post-menopausal women and in more than 50% of men with osteoporosis.[75 76] The impact of these conditions upon the risk of fracture is partly independent from BMD.

Rheumatoid arthritis. Patients with rheumatoid arthritis have a two-fold increase to have osteoporosis when compared to individuals of the same age and sex who do not have RA.[52 77] The relative risk of fracture associated with RA has been estimated at 1.6 to 2.0 for hip, 2.4 for vertebral fractures and 1.5 for humerus fractures.[62 78] This increased risk may be explained by several factors, including reduced exercise and sun exposure, use of glucocorticoids and the catabolic effects of circulating inflammatory mediators.[79 80]

Previous osteoporotic fractures. A history of previous osteoporotic fracture significantly increases the risk of subsequent ones, independently of BMD.[72 81 68] The risk is especially high in the months following the index occurrence and increases with the number of previous fractures. This underlines the need to establish appropriate and timely anti-fracture treatment in all victims of fragility fractures.

Glucocorticoid therapy. Bone loss and increased rate of fractures occur early after the initiation of glucocorticoid therapy and are related to the dosage and duration of treatment,[64] although there seems to be no safe dose in this respect.[65] The rate of fractures in steroid treated patients is higher than expected on the basis of BMD loss alone.[82]

Body mass index (BMI). The age-adjusted risk for any type of fracture increases significantly with lower BMI. The risk ratio per unit higher BMI was 0.97 for all osteoporotic fractures and 0.93 for hip fracture and is independent of age and sex.[51]

Smoking. Current smoking is associated with a significantly increased risk of all kinds of fragility fractures in men and women.[53] On the basis of observational studies, the effects of smoking on the skeleton are at least partially reversible.[83]

Alcohol. Heavy alcohol consumption (≥3 units per day) is associated with a reduction in bone density and increased risk of fracture.[69 56] These effects are mediated through direct, endocrine, metabolic and nutritional effects that converge on the bone.[84] Evidence is scarce regarding the reversibility of fracture risk upon reduction of excessive alcohol intake.[56]

Sedentary lifestyle. Physical activity and fitness reduce the risk of osteoporosis and fracture as well as other fall-related injuries.[58-60]

Falls. More than 90% of osteoporotic fractures occur following a fall,[61] and the self-reported

number of falls during the prior year is associated with an increased risk of osteoporotic fractures.[85] Every year, an estimated 30-40% of patients over the age of 65 will fall at least once.[85]

Vitamin D deficiency. Vitamin D deficiency is extremely common among adults and it has been shown to aggravate bone loss and cause muscle weakness, thus increasing the risk of fracture.[86] Vitamin D can be obtained essentially through exposure to sunlight or food supplements.[67]

Low intake of calcium. Calcium is an essential component of bone. The mean daily requirement has been estimated at 20 mmol (800 mg) per day on Western diets.[87] Vitamin D is essential to guarantee its absorption. A chronically low intake of calcium induces hyperparathyroidism with increased bone resorption and risk of fracture.[63]

Please see Table 3 for a summarized perspective of the impact of different clinical risk factors for fracture.

Table 3. Relative risk of fracture according to the presence/absence of clinical risk factors, while considering or not BMD.

Risk indicator	Without BMD		With BMD	
	RR	**95% CI**	**RR**	**95% CI**
Body mass index (20 vs 25 kg/m^2)	1.95	1.71-2.22	1.42	1.23-1.65
(30 vs 25 kg/m^2)	0.83	0.69-0.99	1.00	0.82-1.21
Prior fracture after 50 years	1.85	1.58-2.17	1.62	1.30-2.01
Parental history of hip fracture	2.27	1.47-3.49	2.28	1.48-3.51
Current smoking	1.84	1.52-2.22	1.60	1.27-2.02
Ever use of systemic corticoesteroids	2.31	1.67-3.20	2.25	1.60-3.15
Alcohol intake > 2 units daily	1.68	1.19-2.36	1.70	1.20-2.42
Rheumatoid arthritis	1.95	1.11-3.42	1.73	0.94-3.20

Reproduced from Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Inte 2005;16(6):581-9.[88]

Prevention strategies for osteoporotic fractures

The prevention of osteoporotic fractures, both at an individual and societal level, encompasses both non-pharmacologic and pharmacologic interventions.

Non-pharmacologic measures include the education of patients and the general population regarding the origins of osteoporosis, with emphasis on modifiable risk factors related to life-style, and its consequences – fractures, death and disability. The promotion of bone-healthy behaviors, capable of decreasing the risk of osteoporosis, falls and fractures, is paramount in this respect. They include adequate calcium and vitamin D intake (or sun exposure), regular

weight-bearing exercise, avoiding smoking and excess alcohol intake and, finally, measures to prevent falls.[17 89] An important aspect, especially at the societal level of intervention, is the promotion of similar healthy habits in children and adolescents as they are essential to assure the attainment of the highest possible peak bone mass early in life.[90] All persons should be stimulated to adopt a healthy balanced diet and a physically active lifestyle beginning from childhood and continuing throughout life, in order to guarantee normal skeletal growth and aging.

As pharmacologic treatment options, we have a variety of medications with different routes and dosing regimens (Table 4). They include bisphosphonates (especially alendronate, risedronate and zoledronic acid), raloxifene, denosumab and parathyroid hormone peptides.[91] Most of these are approved only for the treatment of postmenopausal osteoporosis. However, the bisphosphonates listed above and teriparatide are also approved for the prevention and treatment of glucocorticoid-induced osteoporosis[92] and for the treatment of osteoporosis in men.[93] Strontium ranelate was also approved for these indications but was recently almost abandoned due to cardio-vascular side effects.[94 95]

Table 4. Pharmacological interventions used in the European Union for the prevention of osteoporotic fractures.

Intervention	Year of market approuval	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
Zolendronic acid	2005	5 mg once yearly	Intravenous injection
Denosumab	2010	60 mg twice yearly	Subcutaneous injection
Raloxifene	1998	60 mg once daily	Oral
Bazedoxifene[a]	2009	20 mg once daily	Oral
Strontium ranelate	2004	2 g once daily	Oral
Teriparatide	2003	20 µg once daily	Subcutaneous injection
Parathyroid hormone 1-84	2006	100 µg once daily	Subcutaneous injection

a Registered but not marketed widely (Germany and Spain)

Derived from Strom O, Borgstrom F, Kanis JA, et al. 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). Arch Osteoporos 2011;6:59-155.[91] and reproduced from Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8(1-2):136.[28]

All these interventions have been shown to reduce the risk of vertebral fracture when adequate intake calcium and vitamin D are guaranteed. Of the available options, alendronate, risedronate, zoledronic acid, hormone replace therapy (HRT) and denosumab have been demonstrated to reduce vertebral, non-vertebral and hip fractures (Table 5).[96-107]

Table 5. Anti-fracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomised controlled trials.

	Effect on vertebral fracture risk		**Effect on non-vertebral fracture risk**	
	Osteoporosis	**Established osteoporosis[a]**	**Osteoporosis**	**Established osteoporosis[a]**
Alendronate	+	+	NA	+ (Including hip)
Risedronate	+	+	NA	+ (Including hip)
Ibandronate	NA	+	NA	+ [b]
Zoledronic acid	+	+	NA	+ [c]
HRT	+	+	+	+ (Including hip)
Raloxifene	+	+	NA	NA
Teriparatide and PTH	NA	+	NA	+ [d]
Strontium ranelate	+	+	+ (Including hip[b])	+ (Including hip[b])
Denosumab	+	+[C]	+ (Including hip)	+ [c]

HRT, hormone replace therapy NA, no evidence available; PTH, Parathyroid hormone; +, effective drug;

[a] Women with a prior vertebral fracture; [b] In subsets of patients only (post hoc analisys); [c] Mixed group of patients with or without prevalent vertebral fractures; [d] Shown for teriparatide only.

Derived from Kanis JA, Burlet N, Cooper C, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2008;19(4):399-428.[10] and reproduced from Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013;24(1):23-57.[22]

Despite the relative efficacy of anti-osteoporotic agents, systematic reviews and meta-analyses[108 109] have shown that the rate of persistence and adherence to treatment is very low: one third to one half of patients do not take their medications as recommended, with many stopping treatment shortly after prescription.[109] Nonadherence has been shown to result in an increase of risk of fracture.[110] Strategies to increase adherence, such as involving the patient in the therapeutic decisions,[111 112] and engaging other health professionals, namely through fracture liaison services, are dearly needed to improve efficiency.

New strategies for the prevention of osteoporotic fractures: Nursing interventions and Fracture Liaison Services

Compelling research confirms that the vast majority of patients with this disease, worldwide, are not treated or even diagnosed, due to the lack of manifestations of the disease before fracture occurs.[113] Unfortunately, even after fractures take place only a minority of patients

are prescribed with adequate preventive treatment, either at hospital discharge or over the following years.[114-117] Research also demonstrates that although patients may have good knowledge of what osteoporosis is, they generally have a low level of understanding of the role of medication in reducing fracture risk, various concerns about its side effects, poor understanding of the causes of osteoporosis, and uncertainty about how it can be controlled.[118]

This situation obviously needs to be changed if we want to curtail the continuous expansion of the burden of osteoporotic fractures. New strategies, involving an enlarged group of health professionals and reliable mechanisms to articulate, foster and monitor their actions are needed. In fact, health care professionals are currently uncertain about their role in this campaign.[117 119 120]

Faced with the reasons for inefficiency listed above, it is forceful to conclude that nursing may play a decisive role in the overall strategy to prevent osteoporotic fractures, for several domains of reasons:

- Nurses are involved in various points of contact within the health care system, providing them opportunities to identify and correct risk factors[121]
- Nurses are, typically, dedicated and efficient experts in communication with patients and family[122]
- Nursing has a well-established record of effective implementation and maintenance of protocolled activities in diverse fields of Medicine[123]
- Nurses are trained in critical thinking, effective communication and interaction with other members of the interdisciplinary team needed to address the problem [124 125]
- Nurses developed their action based on a Patient-centered care which improves health outcomes[126 127]
- Nurses have even been involved in the prescription of treatment to osteoporosis, with good results.[128 129]

In fact, the performance of nurses has been demonstrated to superior to that of physicians in several of these domains, with special emphasis on patient/family education[130 131] and protocol keeping.[132] Nurses may, and should, therefore, be active members of the multiprofessional team involved in the prevention and care of osteoporotic fractures.

The role of nurses in osteoporosis can be envisaged in the following different stages: screening, education for prevention, management, and education after diagnosis. [128 132-135]

These can include the following tasks:

- Incorporating simple questions on risk factors for osteoporosis into standard patient assessments and community questionnaires, in order to improve early detection[122]
- Promoting education regarding bone health to prevent osteoporosis in general population,[136-138] including children, youth and parents[139]
- Providing education to other professional groups regarding bone health[122]
- Implementing screening programs is at-risk-populations[130 140-143 144]
- Assessing the risk of falls in the elderly and promoting preventive strategies[145-147]
- Supporting individuals in the treatment and management of this condition through ongoing assessment, teaching and counselling after diagnosis[148 149]
- Promoting patients' commitment and compliance to lifestyle modifications and treatment over the course of their lives, and to cope with chronic illness through the development of coping strategies and, as required, pain management[129]
- Providing ongoing remote telephone counselling and support[133 150]
- Promoting the compliance and persistence with osteoporosis pharmacologic treatments drugs.[151]

The most recent results have led to a consensus that best strategy to optimize the prevention of osteoporotic fractures and the health and wellness of its victims demands a coordinated and interdisciplinary approach. This can be enhanced by the establishment of an effective fracture liaison services (FLS). These services are usually coordinated by a dedicated nurse specialist, working in orthopedics/rheumatology under the guidance of a medical specialist in bone health. Nurses are often appointed as the key to the success of these services.[152-155] The implementation of such services are likely to raise awareness of osteoporosis among health care providers, confirm patients assessment for risk of fracture, provide and ensure effective preventive and therapeutic management of osteoporosis.[153] Such services may also operate as the headquarters of preventive strategies targeting the general population.[156]

Patient centered care and e-health strategies: the opportunity in osteoporosis

Reducing risks and improving patient health outcomes are requirements currently faced by healthcare systems all over the world.[157] Furthermore, the high costs of health require enhanced efficacy and efficiency of healthcare services provision.[158] Engaging patients in the responsible management of their health is widely acknowledged as a way to answer those challenges. Indeed, patients who are active and effective managers of their healthcare are

demonstrated to obtain more positive clinical outcomes than patients who are disengaged and passive.[159 160] Moreover, there is increasing agreement that strategies based on patient centered care have many benefits and achieved better health outcomes, greater patient satisfaction, promoting appropriate use of services, reduced health costs[161] and are crucial factors for improving quality of care and increasing patient safety.[162]

Patient-centered care is defined as an approach to healthcare that takes into consideration the patient's needs, values, and perspectives when developing a treatment plan with a health professional.[163]

Patient-centered care, also called client-centered care, is considered to be a fundamental component in several diseases.[164] However, despite widespread endeavors over many years, patient-centered care continues to evade some areas of healthcare as for example osteoporosis.[165 166]

A multi-site study performed to evaluate patient preferences for patient-centered care demonstrates that patient-centered care provision should include effective communication, partnership, and health promotion.[167] Effective communication has been defined as the exploration of the patient's disease and illness to develop an understanding of the patient's healthcare experiences.[166] Developing a partnership with patients occurs when health professionals and patients find common ground upon which a healthcare plan can be developed mutually.[161] Finally, effective health promotion, is defined as tailoring healthcare plans based on reflections on the patient's past health history and current health context, helps ensure that healthcare plans are developed from an understanding of previous healthcare experiences.[168]

The democratization of health information, use of social media, rapid growth of networked patient communities, and new technologies have changed the landscape and provide new opportunities to harness the energy and expertise of patients.[164] As so patient centered care programs should integrate new technologies for health (eHealth), that can be utilized to increase patient engagement in the screening of several diseases, which resulted in a higher level of satisfaction, increased understanding of their care, improved engagement, and better compliance to behaviors prescribed by their health professional.[169-173]

The eHealth tools allow to develop integrated, sustainable and patient-centered services and promote effective exchanges among the actors involved in the care process.[174] Many studies show that people who actively seek to learn about and manage their health are more likely to participate in preventive and healthy behaviors, self-manage their health conditions, have better care experiences, and achieve better health outcomes.[175] Many high-quality decision aids, self-management tools, mobile applications, and Internet-based resources can be provided to patients at the time of their office visit, publicity or via a patient portal.[176]

A uniform approach to patient-centered care integrating eHealth in osteoporosis has not yet developed. Understanding current approaches to patient-centered care and patient perspectives on this disease can act as a foundation to future discussions on the development of an osteoporosis specific approach to patient-centered care provision. We currently know, that despite the increased awareness of the magnitude and consequences of osteoporosis and the availability of recommendations for screening and treatment by multiple organizations, osteoporosis is still under diagnosed and inadequately managed, the solution to this problem could consist to develop a program based on patient-centered care and eHealth and create a mechanism that allow involvement of patients and families in their care, with particular focus on caring, patient communication, sharing of control for decisions, and the integration in the decision making process in the guidance of nurses, physicians, and other providers.[177] In chapter 8 of this thesis we propose the creation of a website using a strategy that involve eHealth and the patient centered care approach with the guidance of a team of health professionals lead by a nurse.

In chapter 9 we promote the creation of a fracture liason service based on patient/family centered care. The proposal recommends that a specialist nurse should deliver this service. This recommendations is performed based on the evidence that nurses have an important role in patient centered care programs as they play one of the most important roles in influencing patient perceptions. The delivered of care will be based on the Person-Centred Nursing (PCN) Framework developed by McCormack and McCance in 2006 and 2010[178 179]. In summary, the Framework focus on delivering care through a range of activities and include: working with patient's beliefs and values, engagement, having sympathetic presence, sharing decision making, providing holistic care, to adopt or create systems that facilitate shared decision making, the potential for innovation and risk taking, and the physical environment.[178 179]

Patient-centered care has become a key focus in the delivery of health care. The successful healthcare providers of the future will be those that are able to effectively share the philosophy of patient-centered care. Nurses are natural leaders for patient-centered care initiatives, having first-hand knowledge of what it truly takes to create a safe, positive and satisfying experience.

We hope that adopt such strategies in osteoporosis field will help to increase the screening and management of the disease

Paradigm change in osteoporosis screening and treatment

Several therapeutic options and screening strategies are available to effectively decrease fracture risk.[28 180 181] The main clinical challenge still consists in accurately identifying and

selecting individuals for bone densitometry and for pharmacological treatment, in order to increase efficiency and minimize individual and societal costs.[6]

Until recently, the strategy to prevent fractures was essentially based on the performance of DXA and verification of the WHO densitometric criteria: those with normal or osteopenic values were given preventive measures, those with osteoporosis were additionally eligible for pharmacological treatment.[7] In summary: the diagnostic criteria were taken as the intervention criteria. In some recommendations, this dichotomous concept was blended with a qualitative consideration of risk factors, their presence advising treatment even for people with osteopenic T scores.[182 183]

The limitations of this approach were well-recognized. In fact, most fractures occur among people with BMD values in the non-osteoporotic range, who would be excluded from treatment under this paradigm.[24] Additionally, several risk factors for fracture were identified which were independent of BMD.[70] A good example is age: a woman that keeps the same T-score from age 50 to 80 will see her risk of fracture increase 5 to 10 fold just as an effect of age.[184 185] Another example is given previous fractures or family history of hip fracture (See Table 3).[52 186] Therefore, the need to use clinical risk factors in addition to BMD T-scores was obvious.

Moreover, both BMD and clinical risk factors could only provide a relative risk of fracture, per comparison with a similar person without that particular feature: by considering these without additional information we might estimate how many fold higher was the risk of one person in comparison to another, but have no formal concept of the actual risk of any of the two. Clinical decisions, however, must be based on absolute risks of an event, and these could only be obtained if the relative risks were applied upon the background epidemiology of fragility fractures in a similar context.

This need led, though numerous and careful meta-analyses of data on risk factors, to the development of risk assessment tools, which can be used to estimate the future absolute fracture risk in the individual patient, based on clinical variables, with or without DXA. The most widely used of these is the FRAX®, but others have been developed, including the QFracture® and the Garvan risk calculator.[187]

The FRAX®, launched in 2008, was developed by the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK. It is an algorithm that estimates the probability of a fragility fracture occurring in a given individual over the subsequent 10 year, based on clinical risk factors (age, body mass index and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term oral glucocorticoids, rheumatoid arthritis, causes of secondary osteoporosis and alcohol consumption).[52] It may be performed with or without information on BMD and takes into

account mortality in the same population, as a competing risk. All of these risk factors have been shown to be significant predictors of fracture in the presence or absence of BMD, values, although their specific impact varies according to whether BMD is or not considered.[88] This algorithm is available online, with country specific calibration to the national epidemiology of fracture and mortality of many countries. A very recent systematic literature review about intervention thresholds based on FRAX® found that more than 120 guidelines or academic papers incorporated FRAX® for decision making in clinical practice.[187]

Once such a model is established for a given population, it becomes possible to define levels of risk that justify or recommend further investigation or therapeutic intervention. The intervention threshold becomes separate from the diagnosis threshold. And this is quite appropriate as some people with osteoporosis will have a low risk of fracture over the next following years (i.e., young people) while others without the densitometric criterion will have an elevated risk justifying intervention (due to other risks factors, such as age or family history).

In 2008, National Osteoporosis Foundation (USA)[188] recommended pharmacologic intervention for a people with a 10-year fracture probability ≥3 % for hip or ≥20% for major osteoporosis-related fracture. This was established on the basis of cost-effectiveness analyses. In the same year, the National Osteoporosis Guideline Group (UK)[189] recommended that treatment should be initiated for all people whose 10-year FRAX® estimated risk is equal or superior to that of a female patient of similar age, who has already suffered a fragility fracture. This resulted in an age-variable threshold for intervention: eg. treatment is recommended for women aged 50 with an estimated ten-year risk of major fracture >7, but for women aged 80 the risk will have be higher that ~25% to grant treatment. Other countries, Canada,[190] France[191], Greece[192] and Switzerland[193] have, since then, also defined their recommendations based on intervention thresholds on FRAX®.

The FRAX® model represents an added value in the selection of the populations to be treated, allowing considerable efficiency gains[194-196] and it may avoid the need for bone densitometry in a large proportion of patients. The use of these assessment tools to estimate the risk of fractures is expected to solve significant constraints in the prevention, screening and management of osteoporosis and osteoporotic fractures.[197]

The simplicity of the FRAX® tool could also lead to the creation of programs were patients can calculate their 10-year fracture probability and promote an approach based on patient centered care.

Osteoporosis and osteoporotic fractures in Portugal. State of the art by 2012

The following paragraphs describe the epidemiological knowledge and the recommendations for screening, prevention and treatment of osteoporosis and osteoporotic fractures in Portugal, at the time we started the work presented in this thesis.

Portuguese participation in the EVOS study, though the University Hospital of Oporto had revealed that 13.5 of Portuguese women and 16.6% of men aged 50-79 years had at least one prevalent vertebral deformity (probable fragility fracture). [198]

The prevalence of densitometric osteoporosis in a random sample of Coimbra municipally (The SAOL Study), studied between 1997-98, including DXA measurements of the femoral neck, was 31.7% in women and 24.7% in men over the age of 50, taking the reference values for T-scores of the densitometer. The average peak bone mass, in this sample, differed significantly from the reference values provided by the manufacturer of the measuring device or by the official USA reference (NHANES III), thus introducing systematic errors in the calculation of T-scores, of up to -0,7 by using the equipment's reference. Naturally the prevalence of osteoporosis depended on the reference used. In fact, the values described above were reduced to 1.7 and 8%, respectively, when our own gender-specific peak bone mass reference was used to calculate T-scores. Notwithstanding the importance of these observations and discussions, it must be recognized that in the absence of actual fracture data and their relationship with BMD, no definite conclusion could be taken as to the best reference in our population. This conundrum, however, becomes irrelevant in face of the research described below.

The incidence of hip fractures (the only with reliable data in Portugal)[199] [200] had been projected to be between 154 to 572 per 100,000 women/year and 77 to 232 per 100,000 men/year, in the period 2000-2002, based on the National Register of Hospital Discharges, [201] one of lowest in Europe.[28] A remarkable geographical discrepancy in age-adjusted rates of fracture was described, with some regions having 3 times higher rates than others (Figure 5).[201] On the basis of the SAOL study described above, the follow evidence supporting was published:

1. That published algorithms to select post-menopausal women[202] or men[203] for DXA (OST, OSTA, BWC and Age) available by then, performed well in the Portuguese population[202]
2. The use of a nationally adapted strategy to select women for DXA, this being recommended for all women aged 65+ or younger than that if body weight <70Kg [202]
3. The use of a nationally adapted strategy to select men for DXA on the basis of available algorithms but using different cut-offs, we had validated for our population (eg. OST <3, OSTA <3, Body Weight <75Kg) [203]

4. That prediction of fractures is specific for gender and site of BMD measurement. This challenges the use of similar algorithms for men and women as well as the use of hip BMD data to accurately estimate future vertebral fracture risk, as done by FRAX®.[204]

The number of hip fractures has been increasing in Portugal: 5,600 in 1989; 6,718 in 1994; 8,500 in 2000; 9,523 in 2006, according to the National Health Directorate.[205] Vertebral, forearm and humerus fractures were also estimated to be increasing.[206] Health authorities calculated that 40.000 osteoporotic fractures occurred in Portugal in 2006, with over 30.000 being non-hip fractures.[205] The scenario for the future was portrayed, as everywhere, as even worse: it is expected that until 2060 life expectancy at birth will increase by about 10 years in Portugal[207], which is expected to fuel an increasing burden of osteoporosis.

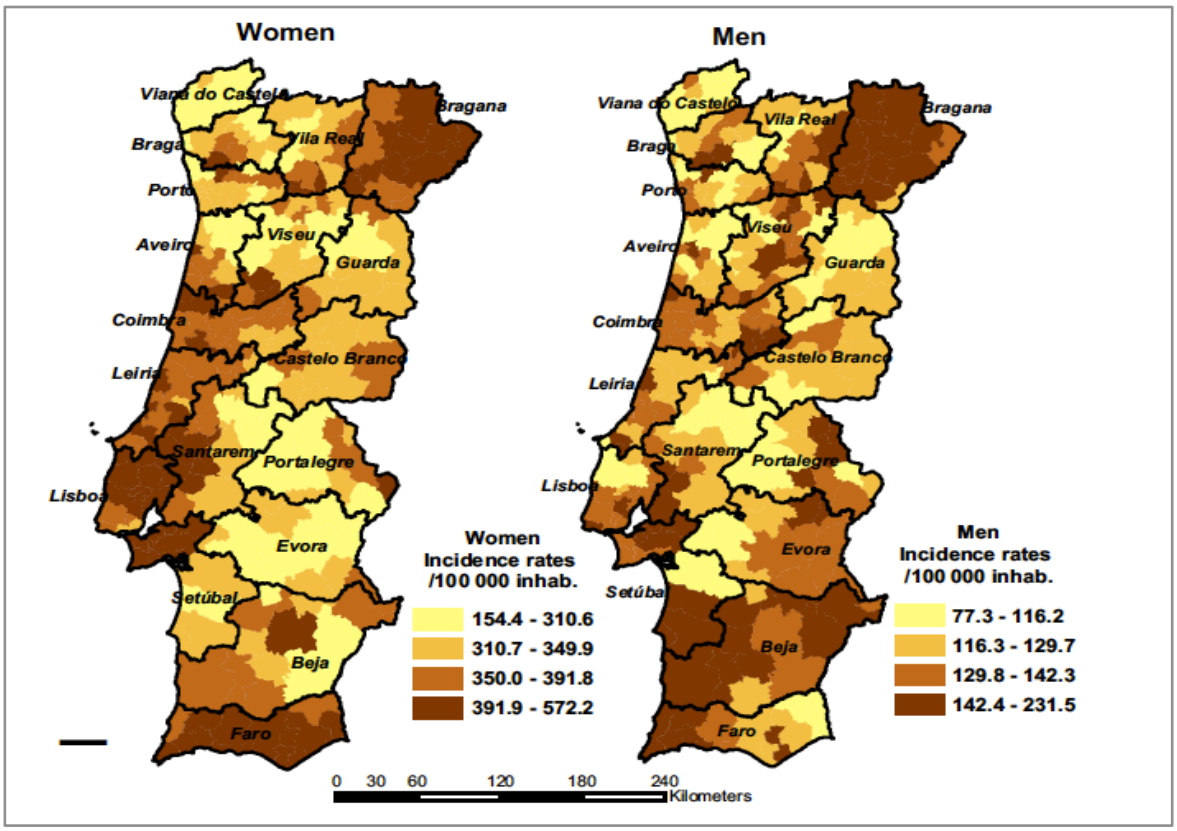

Figure 5. Geographic distribution of age-standardized incidence rates in Portugal (annual average).

Reproduced from de Pina MF, Alves SM, Barbosa M, et al. Hip fractures cluster in space: an epidemiological analysis in Portugal. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;19(12):1797-804.[201].

Few data were available in Portugal regarding the socio-economic impact of osteoporosis and osteoporotic fractures. Available studies are from small regions (hospital area coverage), only for hip fractures, and mainly retrospective with several other limitations.

It was described that 50 to 60% of Portuguese victims of hip fragility fractures lost their ability

to walk after discharge, only 30 to 40% returned to pre-fracture functional status [208 209] and more than 75% became totally dependent thereafter.[210]

Regarding cost and mortality, there were no studies of national or regional representation. In a prospective study performed by Centro Hospitalar of Alto Minho (Ponte de Lima), with 184 patients with hip fracture admitted in 2007, an overall 12-months mortality of 26.8% (48.3% in males and 22.2% in females) was described.[210]

Some studies focused on re-fracture rate and hospital re-admissions. A retrospective study performed at Hospital Curry Cabral (Lisbon) including patients that suffered hip fracture between years 2003 and 2009, found that 3.2% had a new fracture within 5 years (70% of these in the first three years).[211] Another retrospective study performed at Centro Hospitalar das Caldas da Rainha, with 267 patients with hip fracture between 2004 and 2006, found a 231% increase in the probability of hospital re-admissions.[212]

In relation to financial costs, data was also scarce in Portugal. Studies in two tertiary care hospitals indicated that osteoporotic fractures justified more costs, in terms of government allowances for uniform diagnostic groups than myocardial infarctions, chronic obstructive pulmonary diseases and alcohol-associated liver disease[213 214]

The Portuguese Health Directorate estimated that in 2006, 52 millions of euros were spent in direct costs to treat 9,523 hip fractures[215], an amount that had been estimated at 11 millions euros.[216] Based on theoretical modeling through expert interviews, a pharmaco-economic study conducted by the National School of Public Heath[217] calculated the following costs for each fracture in Portugal by 2010, in the perspective of the National Health Service : hip - 8.486€, spine - 1.792€, wrist - 1.044€, proximal umerus 2.914€. An another study by the same by the same school, concluded that in 2009 EUR 2.5 million were spent in long-term care of elderly women, of which 90% (2.2 million) were attributable to osteoporotic fractures, especially of the hip.[209]

The FRAX® tool was launched in 2008 by WHO and by March of 2012 a total of 50 models adjusted for countries and/or ethnic groups were available online.[28] Portugal was not one of them. Health professionals caring for osteoporosis were advised, and still are, to follow the Portuguese Recommendations for the Diagnosis and Treatment of Osteoporosis published in 2007,[218] and the Norms of Clinical Orientation on DXA request (dated 2010)[219] and treatment of osteoporosis dated 2011.[220] These documents recommended DXA as the central piece of diagnosis and decisions regarding treatment. Decisions were also informed by the consideration of clinical risk factors, qualitatively described as major (e.g.: age >65, previous fragility fracture, family history of hip fracture, early menopause, …) or minor (e.g.: rheumatoid arthritis, smoking, heavy drinking, …). No quantitation of their specific impact (relative risk) was provided. DXA examination was recommended in the presence of 1 major

risk factor or 2 minor risk factors. Pharmacological treatment was recommended for people with a previous fracture, or DXA T-score <-2.5 or T-score >-2.5 <-1.5 and major risk factors. The NOC from 2011 made reference to FRAX® without recommending its quantitative application.

The limitations of using a T-score based approach were discussed above. Furthermore, in the absence of precise data on the background probability of fracture the consideration of risk factors could only, at best, result in qualitative, relative risk, considerations. Classifying risk factors qualitatively without indexing them to a relative risk kept clinical decisions in the realm of educated guessing or pure “gut feeling”.

Aims

The work presented in this thesis was intentionally designed to change the previously described status of fragility fracture prevention in Portugal and ultimately to reduce the burden of osteoporotic fractures upon our society. In order to achieve this we set out seven main objectives:

1. To select, through assessment of all relevant evidence, the best fracture prediction tool to apply to the service of our population
2. To build, according to the epidemiology of osteoporotic fractures and mortality rates in Portugal, the national reference to be used in FRAX® to predict the risk of fracture (FRAX®-Port)
3. To assess, and hopefully demonstrate, the accuracy and validity of the FRAX® Port and its individual items in prospective national cohorts
4. To study the costs, health related quality of life and mortality of osteoporotic hip fractures in Portugal
5. To identify, on that basis, the FRAX® Port-based 10-year probabilities of major and hip fractures (with and without BMD) above which pharmacologic interventions are cost effective in Portugal
6. To establish Portuguese national consensus recommendations regarding the indication to perform DXA and to initiate medication aimed at the prevention of fragility fractures
7. To increase the awareness of the general population in general and health professionals in particular to the importance of osteoporosis and for the determinants of rational therapeutic decisions
8. To contribute to the establishment of Fracture Liaison Services, or equivalent systems, in the Portuguese National Health Service.

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Chapter 2

THE ACCURACY OF OSTEOPOROTIC FRACTURE RISK PREDICTION TOOLS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Marques A, Ferreira RJ, Santos E, Loza E, Carmona L, da Silva JA. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. Ann Rheum Dis. 2015; 74(11):1958-1967.

This article was “Editor’s Choice”, deserving the “Editorial” (Lems WF. Fracture risk estimation may facilitate the treatment gap in osteoporosis. Ann Rheum Dis. 2015; 74(11):1943-1945.) and a “Lay Summary Supplement” (“Simple tools predict whether people will suffer from osteoporotic fractures”, available at http://ard.bmj.com/content/suppl/2015/08/06/annrheumdis-2015-207907.DC2/annrheumdis-2015-207907supp_Laysummary.pdf) by the same journal, and a “Medscape Medical News” (Kelly, JC. FRAX, GARVAN Seen as Best for Predicting Fracture Risk. October 21, 2015, available at http://www.medscape.com/viewarticle/852986).

ABSTRACT

Objectives

To identify and synthesize the best available evidence on the accuracy of the currently available tools designed to predict fracture risk.

Methods

We systematically searched PubMed MEDLINE, Embase and Cochrane databases up to 2014. Two reviewers independently selected the articles, collected data from the studies, and carried out a hand search of the references of the included studies. The Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) checklist was used, and the primary outcome was the Area Under the Curve (AUC) and 95% confidence intervals (CI), obtained from ROC analyses. We excluded tools if they: a) had not been externally validated, b) were designed for specific disease populations. Random effects meta-analyses were performed with the selected tools.

Results

Forty-five studies met inclusion criteria, corresponding to 13 different tools. Only three tools had been tested more than once in a population-based setting: FRAX® (26 studies in 9 countries), GARVAN (6 studies in 3 countries), and QFracture® (3 studies in the UK, 1 also including Irish participants). Twenty studies with these three tools were included in a total of 17 meta-analyses (for hip or major osteoporotic fractures; men or women; with or without BMD).

Conclusions

Most of the 13 tools are feasible in clinical practice. FRAX® has the largest number of externally validated and independent studies. The overall accuracy of the different tools is satisfactory (>0.70), with QFracture® reaching 0.89 (95% CI 0.88-0.89). Significant methodological limitations were observed in many studies, imposing caution on the comparison of the tools based solely on AUC.

INTRODUCTION

The major clinical consequence of osteoporosis is the occurrence of fragility fractures.[1] Osteoporotic fractures lead to significant suffering, disability and mortality amounting to enormous costs for individuals and society.[2] Predicting the absolute risk of osteoporotic fractures is, therefore, of utmost importance to optimize prevention strategies.

The World Health Organization provided an operational definition of osteoporosis as a bone mineral density (BMD) that lies 2.5 or more standard deviations below the average value for young healthy women of the same gender and ethnical background [T-score ≤ −2.5].[3-5] However, BMD has limited sensitivity and specificity in the prediction of fracture.[6-8] In fact, a large number of conditions have been firmly established as risk factors for the occurrence of fragility fractures, independently from BMD, including age, gender, body mass index, family history of fractures, ethnicity, premature menopause, glucocorticoid use, rheumatoid arthritis, hyperthyroidism, hyperparathryoidism, Cushing's, anorexia nervosa, malabsorption, falls, previous fractures, smoking, high caffeine intake and alcohol abuse.[9-16] These have been combined into prediction algorithms to estimate fracture probability. When applied upon the baseline epidemiology of fragility fractures in a given population, these algorithms or tools provide estimates of absolute risks. The use of these tools, combined with intervention thresholds, is recommended by many international treatment guidelines.[17-19] However, the existing tools differ in many relevant aspects: from their own feasibility, to the number and availability of clinical risk factors included, the accessibility of BMD measurements and, finally, their performance in different settings. Such diversity calls for an integrative systematic review, as a basis for the critical appraisal and selection of tools to be used in clinical practice and research. The existing reviews[20-23] have a number of important limitations, such as exclusion of males, disregard of some relevant prediction algorithms, lack of meta-analysis where applicable and, naturally, omission of important subsequent publications.

The aim of this systematic review (SR) and meta-analysis is to bring together and describe all relevant evidence on the structure and performance of the currently available tools to predict fracture risk in the general population, while overcoming the previously described limitations.

METHODS

This study was conducted in agreement with the guidelines of the Cochrane Collaboration and our findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[24 25]

Protocol and registration

The reviewers (AM, RF) and a mentor (JAPS) established the protocol of this SR. Advanced technical advice was obtained from experts (LC, EL, ES). This protocol was not published, but it is available upon request.

Eligibility criteria

We established the following inclusion criteria for studies:

i) Population – general adult population, both men and women
ii) Intervention/Test - any fracture risk prediction tool, score, algorithm or other instruments available to predict risk of fracture (with or without BMD measurement)
iii) Comparator/Control – because we aim to evaluate the performance of prediction tests, we defined the observed occurrence of the event of interest - osteoporotic fracture – as the "gold standard"
iv) Outcome/Performance – the primary outcome measure was the Area Under the Curve (AUC) of the fracture risk prediction and its standard error (SE), obtained from Receiver Operating Characteristic (ROC) analysis, in the predetermined prediction time-interval. This was chosen as the primary outcome because AUC represents the accuracy of the predictive model, i.e. the probability that a randomly chosen subject with fracture is correctly rated or ranked with greater risk than a randomly chosen individual without fracture [26]
v) Design - cohort studies (either prospective or retrospective) and case-control studies if past data was available for all subjects.

Osteoporotic fracture risk prediction tools were only included in the final analyses if they were developed from an initial population (derivation model) and then externally validated in a different population (validation model), to prevent overvalued accuracy. Studies that included only specific disease populations (e.g. chronic renal failure or rheumatoid arthritis patients) were also excluded. We also excluded studies that considered the performance of single variables, such as weight or age. We accepted the definition of "major osteoporotic fracture (MOP)" adopted by each tool (See below).

Information sources

We searched only published articles. One reviewer (RF) performed the electronic search, piloted in PubMed MEDLINE (2003-2014) and then adapted to run also in Cochrane (2003-2014) and Embase (2003-2014). The last search was run on February 28th 2014, with monthly automatic e-mail updates until September 6th 2014. We supplemented electronic searches by checking references cited in published SR and in the articles extracted from the electronic searches. Conference abstracts and unpublished studies were not searched.

Search and study selection

The search strategies included free terms and medical descriptors (e.g., MeSH terms) for each PICOD synonym. Some terms used were: Osteoporosis, "Osteoporotic fractures", "Risk Assessment", Algorithms, "Area Under Curve", "Sensitivity and Specificity", "Validation Studies" and "Cohort Studies". The complete electronic string used for PubMed is provided in supplementary Table S1.

The following limits were applied: a) articles published after 2003 (as no such studies had been published before then); b) written in English, Spanish, French, Italian, or Portuguese; and c) performed in Humans.

Studies were screened for inclusion over three phases, using Endnote® software: 1) we searched and deleted duplicates; 2) two authors (AM & RF) independently assessed the electronic search results. They first screened by title and then by abstract. When a title seemed relevant, the abstract was reviewed for eligibility; 3) if any doubt remained, the full text of the article was retrieved and discussed. Arbitration by a third author (JAPS), applied in case of persistent disagreement, took place in two cases. The reason for exclusion was recorded after the full text screening. The inter-rater agreement between AM and RF for the selection based on title, abstract and full text, measured with the Kappa statistic, was 0.99, 0.90 and 0.98, respectively.

The meta-analysis only included articles satisfying, cumulatively, the following 4 criteria: 1) only validation studies were considered (not the derivation models of the tool); 2) the tool had been validated for the country where the study was performed; 3) the tool had been validated for the outcome of the study (e.g. studies employing in the prediction of vertebral fractures, a tool that had only validated to predict hip fractures, were excluded); 4) Data reported on at least 100 fracture events (as recommended by Vergouwe et al.[27]).

Data collection

All the field researchers (AM, RF, ES, EL, LC, and JAPS) validated the data extraction form, which was pilot-tested for feasibility and comprehensiveness with five studies and submitted to consensual minor adjustments. The data was extracted by one author (AM) into a Microsoft Excel® spreadsheet. Data included the general characteristics of each study and the outcomes measured. A second author (RF) confirmed all the data extracted. We contacted some authors in order to obtain additional information, namely regarding required outcome statistical data (confidence intervals and/or SE of AUCs).

Data items

We collected the following: 1) study (authors, year, country); 2) methods (study design, inclusion and exclusion criteria, tool(s) evaluated, factors/variables included into the fracture risk estimation, duration of follow-up, adjustment for time of follow-up, number of participants at the start and at the end of follow-up, reasons of loss to follow-up); 3) participants' characteristics (age, sex, race, diseases, medication); 4) fracture characteristics (number per site, ascertainment methods); 5) outcome results for i. all fractures, ii. major and iii. hip fracture (AUC and SE or 95% confidence intervals).

Risk of bias in individual studies

The quality of each study was independently appraised by two investigators (AM and RF) using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) checklist,[28] and disagreements were solved by a third researcher (JAPS). We excluded some of the optional items of this checklist and added some new ones, as recommended by QUADAS authors[29] and described by other groups.[20] This resulted in a total of 14 items, all graded as adequate, inadequate or unclear (supplementary Table S2). This quality assessment was not an inclusion/exclusion criteria for the meta-analysis, except for item 19, that refers to a minimum of 100 events of interest.

Summary measures and synthesis of results

For the synthesis of results, data were pooled and meta-analysis performed using the Stata® 12 Software (StataCorp. 2011). All results derived from primary studies (AUC and SE) were subjected to double data entry and the pooled AUC with 95% confidence levels were obtained from random effect meta-analyses by instrument type, fracture site, sex, and whether BMD was included or not.

To test heterogeneity among the studies, the I^2 of Higgins and Thompson was calculated. An I^2 value close to 0% indicates no heterogeneity between studies, close to 25% indicates low

heterogeneity, close to 50% indicates moderate heterogeneity and close to 75% indicates high heterogeneity.[30 31]

RESULTS

We included a total of 45 articles, evaluating 13 different tools. Figure 1 shows the studies flow-chart. We identified 3,546 articles from PubMed MEDLINE, 571 from Embase and 928 from Cochrane, and selected 60 for detailed review, of which 30 were excluded: 15 did not assess fracture risk prediction tools, 12 did not provide information regarding osteoporotic fracture outcome and 3 were systematic reviews. We identified 15 additional articles trough hand search (n=13) and through saved search email updates (n=2). A total of 45 articles were finally included.

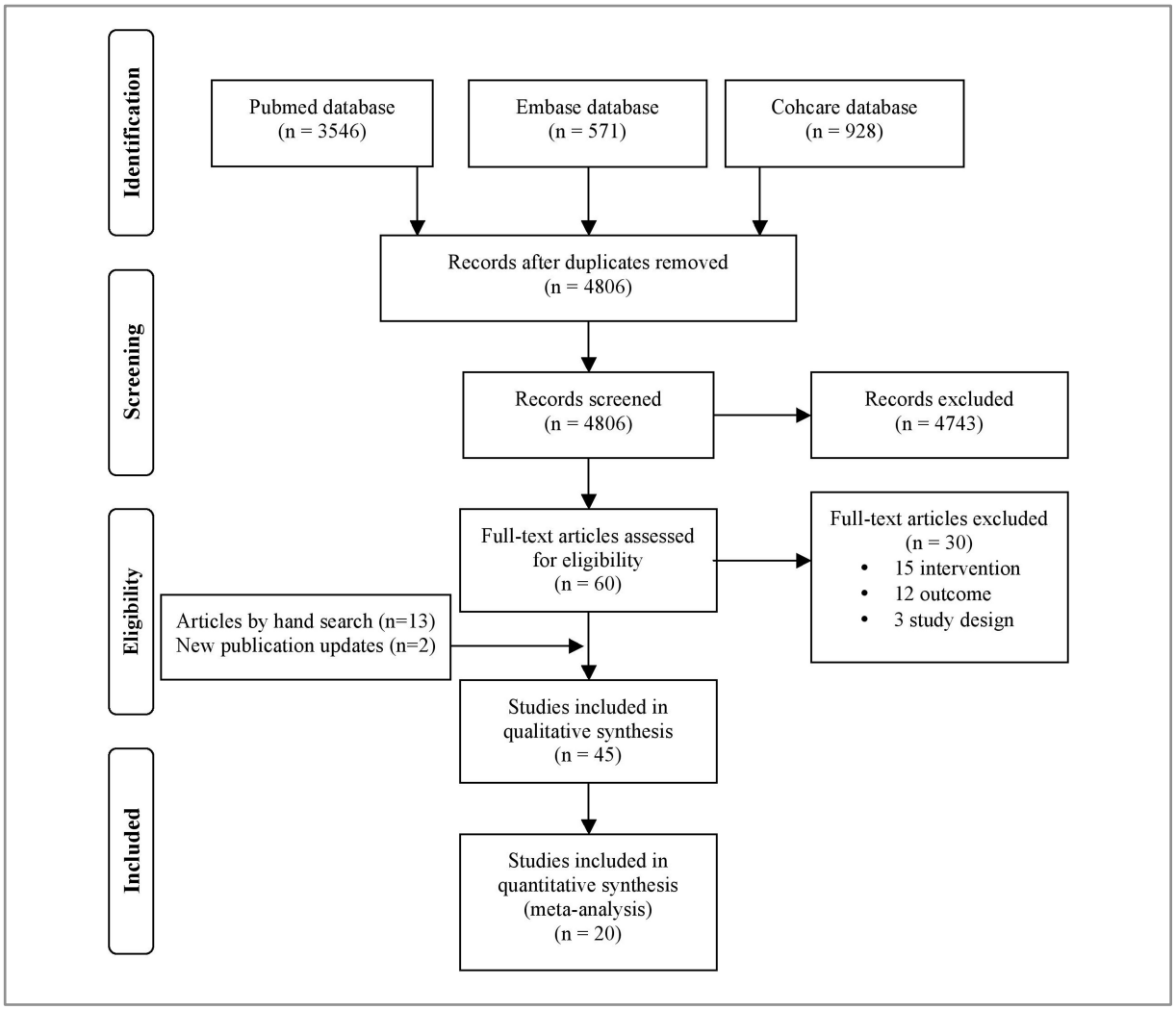

Figure 1. Flow-chart of the selection of article

The main characteristics of the 13 tools identified are presented in Table 1. The number of factors required for calculation varies from 4 in FRAMO to 31 in updated QFracture® (2012) (supplementary Table S3). Seven tools include BMD as a risk factor (two as an optional item). Seven tools only predict fracture risk for women. Some tools are available on the Internet, while others have the algorithm's formula published on the article and some are available only through request to authors. The age range of valid prediction is variable: limited to the interval of 70 to 100 years in FRAMO, to 30 to 99 years in updated QFracture® (2012). Most tools were developed for populations older than 40-50 years. Regarding the time-horizon of prediction, most tools calculate a 5-year (n=7) or a 10-year risk (n=7). FRISC and updated QFracture® (2012) allow the shortest time of prediction (1-year) and some tools provide more than one time-interval, like FRISC with 4 time-points (1, 3, 5 and 10-years), and updated QFracture® (2012) with ten (1 to 10-year). Regarding the types of fracture that are object of separate prediction, 10 of the 13 tools predict hip fractures and 7 predict major or any osteoporotic fractures. The definition of major osteoporotic fractures (MOP) differs between tools. FRAX® considers MOP as the combination of hip, clinical spine, wrist, and humerus.[32] The definition of the updated QFracture® is similar, but all vertebral fractures are included, not only the clinical ones.[33] GARVAN's definition of MOP includes all those considered by FRAX® plus distal femur, proximal tibia/fibula, distal tibia/fibula, patella, pelvis, rib, sternum, hands, and feet (excluding digits).[34]

In addition, FRAMO predicts the mortality risk, and FRISC the immobilization risk. A tool—the "Computer model for osteoporotic fracture risk" —provides an estimation of risk reduction after osteoporosis treatment. Finally, regarding the number of published studies employing each tool, FRAX® (with 26 studies in 9 countries), GARVAN (also known as GRX, 6 studies in 3 countries), and QFracture® (3 studies in the UK, 1 including Irish participants) are the most extensively studied. All other tools have been evaluated by only one or two studies.

Table 1. Characteristics of the fracture risk prediction tools.

Tool	Characteristics				
	Number of clinical risk factors #	**BMD**	**Tool accessibility Gender Age range**	**Prediction time(s) and Outcome(s)**	**Number of studies**
Computer model for osteoporotic fracture risk	8	Yes	Request to authors Female only 45–79	5-yrs Absolute fracture risk Expected absolute risk reduction after treatment.	1 [35]
FRAMO	4	No	Available on article Male/Female 70-100	2-yrs Hip fracture risk Mortality.	2 [36 37]
FRAX®	11	Optional	http://www.shef.ac.uk/FRAX Male/Female 40-90	10-yrs Major osteoporotic fracture risk Hip fracture risk	26 [32 38-62]
FRC	12*	Yes	https://riskcalculator.fore.org/ Male/Female ≥ 45	10-yrs Hip fracture risk	2 [63 64]
FRISC	8	Yes	http://www.biostatistics.jp/prediction/frisc Female only 40-100	1, 3, 5 and 10-yrs Major osteoporotic fracture risk Immobilization risk	2 [59 65]
FRISK	5	Yes	Available on article Male/Female >60	5 and 10-yrs Major osteoporotic fracture risk	2 [66 67]
GARVAN-GRX	5	Optional	http://garvan.org.au/promotions/bone-fracture-risk/calculator/ Male/Female 60-96	5 and 10-yrs Any osteoporotic/ Fragility fracture risk Hip fracture risk	6 [34 39 54 55 68 69]
QFracture®	19	No	Discontinued from website in 2012 Male/Female 30-85	1 to 10-yrs Any osteoporotic fracture risk Hip fracture risk	3 [33 42 70]
Updated **QFracture®** (2012)	31	No	http://www.qfracture.org/ Male/Female 30-99	1 to 10-yrs Any osteoporotic fracture risk Hip fracture risk	1 [71]
Score for estimating the long-term risk of fracture in post menopausal women	8	No	Available on article Female only ≥ 50	5-yrs Clinical vertebral fracture risk Clinical osteoporotic fracture risk Hip fractures risk	1 [72]
Simplified fracture risk system	5	Yes	Available on article Female only ≥ 50	10-yrs Any fracture risk	1 [73]
SOF	14	No	Available on article Female only Age unclear	5-yrs Hip fracture risk	1 [74]
WHI	11	No	Request to authors Female only ≥ 50	5-yrs Hip fracture risk	1 [75]

BMD, Bone Mineral Density. Additional description in supplementary Table S3
*An updated version of the website, dated Sep. 2014, also includes BMD of spine, glucocorticoids exposure, and previous spine fracture, which were not part of the original publication, included in this SR. No further publications supporting this change could be found.

Methodological quality of the studies

A complete assessment of the quality of the 45 studies, using QUADAS-2, as well as a direct comparison between FRAX®, QFracture®, and GARVAN's studies, may be found in supplementary Figures S1 and S2.

supplementary Table S4 shows the main characteristics of the 45 included articles. Thirty-five of the studies had a longitudinal prospective design, 8 were longitudinal retrospective and one was cross-sectional.[66] We also included an RCT.[43] The mean time of follow-up in the prospective cohorts ranged between 2 [36 37 54] and 13.4 years [76] and between 1.7 [55] and 11 (median) [60] in the retrospective ones. Five studies evaluated 2 different tools, and most of them were conducted in North America, Scandinavian and Western European countries, Australia, or Japan. Only two studies were multinational. The exclusion criteria were not described in 10 studies and were scarcely detailed in many others. Only 1 study stated that no exclusion criteria were applied, while the most common exclusion criteria were: unable to walk, use of corticosteroids, bisphosphonates or other bone-active agents, previous history of hip or MOP fractures, hip replacement, and secondary osteoporosis. Participants were mainly recruited from the general population (n=22), but also in osteoporosis screenings (n=12), or were post-menopausal women (n=9). Concerning the total population at baseline, only a study [33] provides this number for both Derivation and Validation Model, while 14 studies do not present the baseline numbers, even for the Validation Model. This number varies from 390 [37] to over one million.[33] All articles provide the number of participants available for event verification. The majority of studies included only women (n=30) while two studies included only men.[45 64] The participant's age in the Validation Model ranged from 30 [33] to 116 years.[32] The numbers of fractures are usually given for hip and/or MOP, but other sites and other specific outcomes are presented according to the tool (e.g. immobilization) [65] or specific aims of the study (e.g. in obese and non-obese).[62] Diagnosis of fractures was based principally by self-report, confirmed by X-rays in 35 studies, or medical records/hospital discharge registers. The highest performances (AUC) were reported for FRAX® in China [41] (Hip_{Women} with BMD=0.88; Hip_{Women} without BMD=0.89) and for "Updated QFracture®" [71] (Hip_{Women}=0.89; Hip_{Men}=0.88). The lowest AUCs ($FRAX®_{Men;\ US;\ MOP}$=0.54; $FRAX®_{Men;\ UK;\ MOP}$=0.57), were reported by a retrospective study using a FRAX® model which had not been validated for that country and with a very small population.[55]

Meta-analysis

A total of 20 articles were selected for the meta-analysis. The reasons for exclusions are described in supplementary Table S5, the most relevant being: number of fractures <100; AUCs provided only for specific subgroups, e.g. economic status. FRAX® is the tool with greater specification of the outcomes: per site, per gender, with/without BMD. All studies with GARVAN included BMD, while QFracture® excludes this measurement. Thus, we performed 10 different meta-analysis for FRAX® (15 studies), 3 for GARVAN (5 studies) and 4 for QFracture® (3 studies; we did not include updated QFracture® published in 2012, because it only had one external validation study). Regarding the total number of participants included

in the meta-analysis, GARVAN is represented by the lowest numbers, QFracture® is in between and FRAX® has the largest numbers. All meta-analysis showed high-heterogeneity, with the exception of one for FRAX® and one for GARVAN (moderate heterogeneity). Results of all meta-analyses are presented in Table 2. Overall, QFracture® obtained the highest AUCs, above 0.80 in 3 out of 4 studies. The three meta-analyses of GARVAN resulted in AUCs around 0.70. Meta-analyses of studies with FRAX® resulted in AUCs between 0.61 and 0.79.

Table 2. Meta-analyses of fracture risk assessment tool according to outcome specifications.

Tool	Outcome Specifications (BMD/Site/Sex)	Number of Studies	Number of participants	Meta-analysis - Random effect model AUC (95% CI)	Heterogeneity I^2
FRAX® (10 years prediction)	Y/ MOP/ W	n=5 [39 41 43 44 60]	14,224	0.67 (0.64-0.71)*	80.2%*
	N/ MOP/ W	n=7 [39 41 42 44 47 48 76]	24,726	0.65 (0.63-0.68)*	67.6%*
	N/ Hip/ W	n=9 [39 41-44 47 48 53 57]	131,244	0.74 (0.68-0.80)*	94.3%*
	Y/ Hip/ W	n=5 [39 41 44 53 57]	115,611	0.79 (0.73-0.85)*	93.3%*
	N/ MOP/ M	n=2 [45 47]	11,199	0.63 (0.60-0.66)*	0.0%
	N/ Hip/ M	n=2 [45 47]	11,199	0.71 (0.65-0.77)*	40,8%
	Y/ MOP/ B	n=3 [46 51]	276,786	0.63 (0.60-0.66)*	97.1%*
	Y/ Hip/ B	n=3 [46 51]	276,786	0.77 (0.73-0.81)*	69.8%*
	N/ MOP/ B	n=3 [46 51]	276,786	0.61 (0.57-0.64)*	96.3%*
	N/ Hip/ B	n=3 [46 51]	276,786	0.67 (0.61-0.73)*	94.7%*
GARVAN-GRX (10 years prediction)	Y/ Hip/ W	n=2 [68 77]	5,574	0.74 (0.61-0.87)*	88.2%*
	Y/ MOP/ W	n=3 [39 68 69]	6,932	0.70 (0.64-0.75)*	93.8%*
	Y/ MOP/ M	n=2 [68 69]	5,010	0.73 (0.68-0.78)*	59.0%
QFracture® (10 years prediction)	N/ MOP/ W	n=3 [33 70]	1,778,570	0.81 (0.78-0.834)*	97.8%*
	N/ MOP/ M	n=2 [33 70]	1,741,983	0.72 (0.67-0.76)*	99.2%*
	N/ Hip/ W	n=3 [33 42 70]	1,779,154	0.89 (0.88-0.89)*	96.3%*
	N/ Hip/ M	n=2 [33 70]	1,741,983	0.87 (0.86-0.88)*	71.0%

BMD, Bone Mass Density; Hip, Hip fractures; MOP, Major Osteoporotic Fractures (MOPs are differently defined for the different instruments)
Y=With BMD; N=Without BMD; W=Women, M=Men, B=Both sexes.
Moderate heterogeneity: Higgins I^2 ~50%, High heterogeneity, Higgins I^2 ~75%; *p<0.05.

Pooled AUC data regarding Hip fractures is presented in Figure 2. This cannot be done for MOP, as this concept differs between the three tools.

We compared the risk prediction accuracy of excluded against included studies with meta-analysis and we found statistically significant higher AUC of the first ones (data not shown).

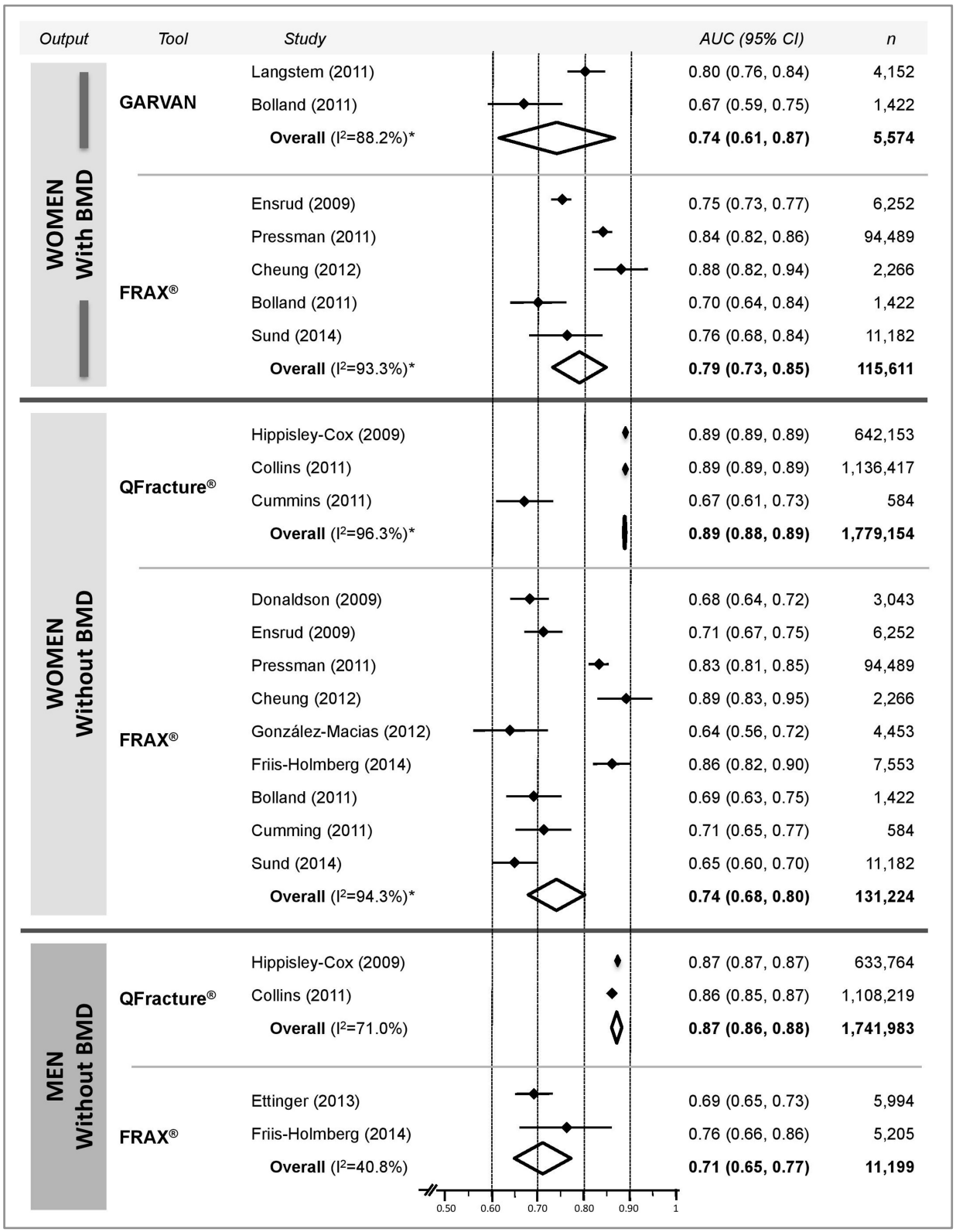

Figure 2. FRAX®, GARVAN and QFracture® pooled AUCs (95% CI) for 10 years Hip fracture prediction, according to sex and BMD input

Summary appraisal of tools

In Table 3 we compare the three different tools in aspects deemed relevant for their selection for clinical and research purposes. Most of them have been presented above.

The diversity of countries and contexts where these three major tools have been tested differ considerably. FRAX® has been adapted to the epidemiology of fracture and death of 57 countries and has been the object of 26 different validations studies in 9 countries. GARVAN was tested only in Australia, New Zealand and Canada. However, it has been proposed that this instrument does not require the incorporation of national fracture data.[34 69] QFracture® was only validated in UK (only 88 participants from another country, Ireland, were included), even if by independent research teams, but, conversely, it has the largest number of participants. QFracture® is associated with the highest AUC, this being achieved at the cost of a greater complexity and lower feasibility, given the large number of risk factors considered.

Table 3. Summary features of the three most studied tools, as deemed relevant for selection of instrument in clinical and research settings.

		FRAX®	**QFracture®**	**GARVAN**
Feasibility	Number of clinical risk factors	11	19	5
	Requirement of BMD	Optional	No	Optional
	Accessibility of algorithm for individual use	Yes	No[#]	Yes
Applicability	Male and female	Yes	Yes	Yes
	Age range	40-90	35-100	50-96
	Prediction intervals	10	1, 2, …, 10	5, 10
	Type of Fracture - Hip	Yes	Yes	Yes
	Type of Fracture - MOP	Yes	Yes	Yes
	Countries	57	UK only	3
	Inclusion in National Guidelines	Yes	Yes	Yes
Validity	Validated in separate cohort	Yes	Yes	Y (BMD only)
	Independent validation §	Yes	Yes	Y (BMD only)
	Number of validation studies	26	3	6[##]
	Population basis for validation – N	4,624,438	3,485,952*	229,162
	Population basis for validation - countries	9[¶]	UK only	3[¶]
	Average quality of studies (QUADAS-2)	Globally similar (see supplementary Figure S2)		
	Duration of follow-up vs tool estimation interval	Yes	Yes (10y only)	Yes (5y & 10y)
	Consideration of national fracture epidemiology	Yes	No	No
	Consideration of background mortality	Yes	No	No
	AUC – Hip, Females, without BMD	0.74 (0.68-0.80)	0.89 (0.88-0.89)	NA
	AUC – Hip, Females, with BMD	0.79 (0.73-0.85)	NA	0.74 (0.61-0.87)
	AUC – Hip, Males, without BMD	0.71 (0.65-0.77)	0.87 (0.86-0.88)	NA
	AUC – Hip, Males, with BMD	0.77 (NA)**	NA	0.85 (NA)**
	AUC – MOP	***	***	***

BMD, Bone Mineral Density; MOP, Major Osteoporotic Fractures; NA, Not applicable/ Not available.
[#]QFracture® was discontinued from the website in 2012. Only the updated version is available now, but this is not suitable to meta-analysis, as it has only been the object of one validation study; [##]Only with BMD; *does not include the updated QFracture® (2012) study; **one study only; ***comparison is inadequate because of different definitions of MOP for each tool; [§]i.e. by independent research groups; [¶]We did not consider the study that included data from 10 countries;

DISCUSSION

This SR identified 13 tools for osteoporotic fracture risk prediction, adding one new instrument (FRISK) [66 67] to the algorithms identified by previous SRs,[20-23] and updating the validation information regarding those already identified. This will help clinicians and researchers select the ones that best apply to their setting and needs. We have also performed a meta-analysis for 10-year risk prediction of hip and MOP fractures with FRAX®, GARVAN, and QFracture® (for men, women, and both genders, with and without BMD). To the best of our knowledge, this is the first meta-analysis on this topic.

The differences between the currently available fracture prediction tools must be underlined, as they impose the need for caution when comparing the results obtained with the different instruments. The number of risk factors considered (which varies between 4 and 31), as well as their nature, will have an important impact on feasibility. Differences in output, regarding sex, age, types of fractures, and time-intervals of prediction, might affect the applicability of the tool. All instruments predict the risk of osteoporotic fractures but not all provide separate estimations for hip and for major fractures.

On the other hand, our quality assessment of the included studies reveals, as it happened with previous evaluations,[20-23] significant pitfalls in most of the studies, although recent publications appear to have better quality.[45 47] Among the most important drawbacks is the lack of certainty of unbiased recruitment from the target population.

There is also a lack of correspondence between the spectrum of participants and the population who is expected to receive the test in daily practice. This problem was observed in about 50% of included studies and in a similar percentage in the reports of the three major tools. All the instruments were validated for the general population, but several studies recruited participants from osteoporosis screening settings,[38 40 42 50-52 55 60 63 72 73] while only some explicitly excluded people treated for osteoporosis.[41 42 53 55 56 58 63] Reports, unfortunately, do not provide the detailed data that would be necessary to assess the potential impact of treatment upon fracture prediction. We also verified that two studies excluded individuals previously exposed to glucocorticoids,[42 43] even though this risk factor was included in the risk algorithm under evaluation.

Follow-up time was consistent with the time-horizon of prediction validated for the tool in only a third of the studies. Furthermore, most of those without the required follow-up time [32 33 40 41 43-45 47-50 53-55 61 62 65 68 70 71] did not perform any statistical adjustments for this, which may influence the estimated AUCs.

Attrition is a well-known problem faced by longitudinal epidemiological studies.[78] The attrition rates vary considerably between the included studies and most of them did not explain these rates. Death is an example of a common cause of attrition in cohort studies of older people,[79] which impacts the accuracy of the models. Only some studies in this SR took that into account.[39 41 45 47 48 57 58 61 62 64] One study [38] excluded women who died during follow-up, even though fracture, or its complications, might have been the cause of death.

For practical reasons we will, hereafter, focus our discussion only on FRAX®, QFracture®, and GARVAN, as only these tools have been the object of more than two validation studies, testing exactly the same algorithm. FRISC has three validation studies, but each of them considered a different number of risk factors.

Both FRAX®, GARVAN, or QFracture® can differentially predict risk in men and women and estimate the risk for hip and MOP. However, the definition of the latter is different in each tool, thus precluding direct comparison.

QFracture® and updated QFracture® (2012) include a larger number and wider variety of clinical risk factors than the others. It is reasonable to predict that algorithms with the longest lists of risk factors will have problems of feasibility and adherence, but also greater accuracy. On the other hand, shorter lists may diminish accuracy of the prediction. In some studies, the authors excluded some of required risk factors and this will inevitably weaken the robustness of the prediction, even if the impact upon the AUC and c-statistic is typically small [80 81]. In fact, even strong risk factors will have a minimal impact on the AUC if their prevalence in the studied population is low. This may be mistakenly reassuring and, as a rule, prediction tools should be used in strict accordance with the instructions provided by the authors, which in turn reflect the conditions of validation. There are, therefore, several potential caveats in the conclusion that deleting risk factors or opting for simpler ones is a good choice on the basis of AUC alone.[82]

In FRAX, fracture probability is computed taking both the risk of fracture and the risk of death into account. Neither GARVAN nor QFracture® included mortality. Kanis *et al.* [82] have shown that this induces an inadequate continuous increase in the risk predicted by GARVAN in very advanced age. It is possible that the same may happen with QFracture®.

Accuracy of estimates

Comparing instruments based on their AUCs, we found important pitfalls related, first and foremost, to differences in the definitions of events and to the participants' characteristics.[82] AUCs also tend to be smaller, the narrower the age range and the longer the duration of follow-up.[82]

To avoid these pitfalls we have: 1. appraised the quality of studies; 2. excluded the original studies, i.e. derivation models from meta-analysis, 3. restricted the comparative analysis to minimally comparable data (hip fractures).

We found that the meta-analysis of studies indicates higher AUCs with QFracture® (0.89 and 0.87) than FRAX® (0.74 and 0.71) when comparable data are available: hip fractures in women and men, respectively, both without BMD. The 95% CI in the main two studies and overall results of QFracture® are practically residual and much smaller than the observed for FRAX® (0.68-0.80 and 0.65-0.77), which reflects the larger number of participants in the studies of QFracture®. QFracture® was designed for integration into electronic records systems where all the necessary data already are collected as part of routine care, as in the clinical research databases that served to derive and validate the model. The tool is incorporated in the electronic system allowing automatic calculation. The setting is very convenient but very hard to reproduce elsewhere. Derivation and validation were performed in different population samples, but coming from the same country, which favours a higher AUC. The fact that the tool amenable to meta-analysis (QFracture® 2009) is no longer available adds to these difficulties.

Adding BMD to FRAX® increases the AUC from 0.74 to 0.79 in women, and to 0.71 to 0.77 in men, but this is still below the values achieved with QFracture® (0.89 and 0.87, respectively). Comparing the meta-analysis for GARVAN and FRAX®, is only possible for hip fractures in women, using BMD – the results indicate a small numerical advantage for FRAX®.

The performance of all these tools was validated for the general population. Thus, their application for specific settings (e.g. osteoporosis population, secondary causes of osteoporosis) implies a risk of error. Further studies should also evaluate the threshold for use in clinical practice. Comparison between tools should, ideally, be made in the same population.

Limitations and strengths of this study

Assessing the quality of the studies with QUADAS-2 proved a difficult task, mostly due to poor reporting, and may be controversial in some points.

Regarding to the meta-analysis we frequently had to calculate the standard error (SE) based on other parameters, which may have led to slightly different results (at a centesimal level).

We did not request authors to provide data on age when this was missing from the publications. This may have a slight influence on the results of meta-analysis, has age may affect the AUC.[82] The only way to adjust our meta-analyses by age was to include studies

with similar age-bands or to stratify. We did the first but not the latter, as it was not possible to stratify with the published data.

Using AUC as outcome for the meta-analysis could also be seen as a limitation, given its fragilities as discussed above. Furthermore, given that fracture rates differ significantly from country to country, comparison of data obtained in different countries involves some risk of error. However, the vast majority of studies only provide this data.

Among the strengths of this study we would underline the comprehensiveness of the literature search and appraisal. Although we did not include the so-called "grey literature" (i.e. congress abstracts and unpublished data), hand search gives us a high confidence that no major studies have been disregarded. No study was excluded for language reasons. We limited our meta-analyses to sets of data that we found to be valid and directly comparable, thus avoiding most of the potential errors in similar exercises. Because we recognized significant heterogeneity, the analyses were performed using the random effects model,[30 31 83] which assumes that the effect of interest is not the same in all studies. This is a more conservative approach, resulting in wider 95% confidence levels while, hopefully, reducing the risk of unrealistic assumptions.[30] This was the first meta-analysis performed on data from fracture risk prediction tools.

CONCLUSIONS

Thirteen externally validated algorithms designed to predict the osteoporotic fracture risk are currently available to clinicians and researchers. Most of these tools are feasible in clinical practice and are of simple access and use. FRAX®, QFracture®, and GARVAN are the most extensively studied tools, with FRAX® having the greater number of independent studies. FRAX® was evaluated in a larger number of countries and also allows a finer specification of outcomes. Adding BMD to FRAX® increases the AUC for hip fractures in both men and women. Studies with QFracture® present the highest AUCs; however, it has only been studied in the UK and Ireland and requires the consideration of 19 clinical factors. The number was actually increased to 31 in the updated version, with a marginal increase in accuracy.

Methodological limitations and risk of bias are present in most studies but to a lower extent than previously shown. High-quality studies to assess the calibration of prediction fracture tools are still needed. Researchers should use the instruments respecting the requirements and indications for which they were validated, in order to allow international unbiased comparisons and better quantitative synthesis.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Search Strategy in PubMed MEDLINE

(((((("Osteoporosis"[Mesh] OR Osteoporoses OR Osteoporosis, Senile OR Osteoporoses, Senile OR Senile Osteoporoses OR Senile Osteoporosis OR Osteoporosis, Age Related OR Osteoporosis, Age Related OR Bone Loss, Age Related OR Age Related Bone Loss OR Age Related Bone Losses OR Bone Loss, Age Related OR Bone Losses, Age Related OR Age Related Osteoporosis OR Age Related Osteoporosis OR Age Related Osteoporoses OR Osteoporoses, Age Related OR "Osteoporosis, Postmenopausal"[Mesh] OR Perimenopausal Bone Loss OR Bone Loss, Postmenopausal OR Bone Losses, Postmenopausal OR Postmenopausal Bone Losses OR Osteoporosis, Post Menopausal OR Osteoporoses, Post Menopausal OR Osteoporosis, Post Menopausal OR Post Menopausal Osteoporoses OR Post Menopausal Osteoporosis OR Postmenopausal Osteoporosis OR Osteoporoses, Postmenopausal OR Postmenopausal Osteoporoses OR Bone Loss, Perimenopausal OR Bone Losses, Perimenopausal OR Perimenopausal Bone Losses OR Postmenopausal Bone Loss OR "Decalcification, Pathologic"[Mesh] OR Decalcification, Pathological OR Pathological Decalcification OR Pathologic Decalcification OR Involutional Osteoporosis Primary Osteoporosis OR Bone Fragility Endocrine Osteoporosis OR Osteoporotic Decalcification OR "Bone Density"[Mesh] OR Bone Densities OR Density, Bone OR Bone Mineral Density OR Bone Mineral Densities OR Density, Bone Mineral OR Bone Mineral Content OR Bone Mineral Contents OR BMD OR Bone mineral density[All Fields] OR (low bone mass) OR (low bone mass density) OR (low bone mineral density) OR (low bone mass premenopausal women) OR (low bone) OR (low bone density) OR (postmenopausal bone loss) OR (bone loss osteoporosis) OR (bone loss postmenopausal) OR (bone loss)))) AND (("osteoporotic fractures"[MeSH Terms] OR fracture, Osteoporotic OR Fractures, Osteoporotic OR Osteoporotic Fracture OR "Fractures, Bone"[Mesh] OR Broken Bones OR Bone, Broken OR Bones, Broken OR Broken Bone OR Bone Fractures OR Bone Fracture OR Fracture, Bone OR Fracture OR (hip fracture)))) AND (("Questionnaires"[Mesh] OR Questionnaire OR Questionnaire Design OR Designs, Questionnaire OR Designs, Questionnaire OR Questionnaire Designs OR NOF OR (National Osteoporosis Foundation) OR SCORE OR (Simple Calculated Osteoporosis Risk Estimation) OR ORAI OR (Osteoporosis Risk Assessment Instrument) OR ABONE OR (Aged Body Size No Estrogen) OR FRAX OR (fracture risk assessment tool) OR (FRACTUREindex) OR ("FRACTURE index") OR OSTT OR (Osteoporosis Self assessment Tool) OR "OST (OSTA)" OR DOEScore OR (Dubbo Osteoporosis Epidemiology Study) OR FOSTA OR (Female Osteoporosis Self assessment Tool for Asia) OR Self-assessment Tool OR SOFSURF OR EPIDOS study OR EPIDemiologie de l'OSteoporose OR EPIDOS fracture study OR Weight only EPIDOS OR "WOE" OR FNBMD OR "Bone mineral density at the femoral neck") OR "pBW" OR IOF OR (International Osteoporosis Foundation) OR Garvan OR KKOS OR OSIRIS OR DVO OR MORES OR Qfracture OR QFractureScores OR "Risk Assessment"[Mesh] OR Assessments, Risk OR Risk Assessments OR Assessment, Risk OR Risks and Benefits OR Benefits and Risks OR Benefit Risk Assessment OR Assessment, Benefit Risk OR Assessments, Benefit Risk OR Benefit Risk Assessment OR Benefit Risk Assessments OR Risk Benefit Assessment OR Assessment, Risk Benefit OR Assessments, Risk Benefit OR Risk Benefit Assessment OR Risk Benefit Assessments OR "Risk Factors"[Mesh] OR Factor, Risk OR Factors, Risk OR Risk Factor OR Risk index OR Risk score OR Risk stratification OR "Risk"[Mesh] OR Risks OR Relative Risk OR Relative Risks OR Risk, Relative OR Risks, Relative OR scale risk OR clinical risk stratification instruments OR prognostic score OR score prediction OR scoring system OR Screen OR Screening OR "Algorithms"[Mesh] OR Algorithm*)) AND (("Dimensional Measurement Accuracy"[Mesh] OR (Accuracies, Dimensional Measurement) OR (Accuracy, Dimensional Measurement) OR (Dimensional Measurement Accuracies) OR (Measurement Accuracies, Dimensional) OR (Measurement Accuracy, Dimensional) OR "Area Under Curve"[Mesh] OR Area Under Curves OR Curve, Area Under OR Curves, Area Under OR Under Curve, Area OR Under Curves, Area OR AUC OR Harrell's C value OR likelihood ratio OR likelihood positive ratio OR likelihood negative ratio OR ROC curve OR ROC curves OR "Sensitivity and Specificity"[Mesh] OR Specificity and Sensitivity OR Specificity OR Sensitivity OR "Predictive Value of Tests"[Mesh] OR "False Positive Reactions"[Mesh] OR False Positive Reaction OR Positive Reaction, False OR Positive Reactions, False OR Reaction, False Positive OR Reactions, False Positive OR False positive OR False negative OR True positive OR True Negative OR "False Negative Reactions"[Mesh] OR False Negative Reaction OR Reaction, False Negative OR Reactions, False Negative OR "Reproducibility of Results"[Mesh] OR Reproducibility of Findings OR Reliability AND (Epidemiology) OR Reliabilities AND (Epidemiology) OR Validity AND (Epidemiology) OR Validities AND (Epidemiology) OR Validity of Results OR Reliability and Validity OR Validity and Reliability OR Reliability of Results OR "Feasibility Studies"[Mesh] OR Feasibility Study OR Studies, Feasibility OR Study, Feasibility OR Feasibility OR "Validation Studies as Topic"[Mesh] OR construct validity OR validation studies OR validation study OR validity reliability OR reliability validity OR validity OR validated OR validated study OR validated studies OR applicability OR clinimetric properties OR Psychometrics AND "[Mesh] OR Psychometric OR responsive OR responsiveness OR validation[tiab] OR validate[tiab] OR reproducib*[tiab] OR " AND psychometrics AND "[MeSH] OR psychometr*[tiab] OR clinimetr*[tiab] OR clinometr*[tiab] OR reliab* [tiab] OR valid*[tiab] OR reliability validity assessment OR " AND Evaluation Studies as Topic Mesh OR Evaluation OR Evaluations OR Evaluation Indexes OR Indexes, Evaluation OR Use Effectiveness OR Methodology, Evaluation OR Evaluation Methodologies OR Methodologies, Evaluation OR 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Supplementary Table S2. Modified version of QUADAS-2. The checklist was used to assess the study quality. All items were scored with "yes", "no" or "unclear". Items 3-7 and 10 were excluded as they were not considered relevant in the current context. We added 6 new items to the checklist (items 15 to 20) as relevant for our review.

Item		Yes	No	Unclear
1.	**Was the spectrum of patients representative of the patients who will receive the test in practice?** *(Unselected patients recruited from the general population?)*	( )	( )	( )
2.	**Were selection criteria clearly described?** *(Clear definition of the criteria used in- and exclusion criteria for entry into the study)*	( )	( )	( )
3.	~~**Is the reference standard likely to correctly classify the target condition?**~~			
4.	~~**Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?**~~			
5.	~~**Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?**~~			
6.	~~**Did patients receive the same reference standard regardless of the index test result?**~~			
7.	~~**Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?**~~			
8.	**Was the execution of the index test described in sufficient detail to permit its replication?** *(Was the tool/tools described in sufficient detail to permit its replication (a final algorithm)?)*	( )	( )	( )
9.	**Was the execution of the reference standard described in sufficient detail to permit its replication?** (*Was the fracture collection verified and not only self-reported?)*	( )	( )	( )
10.	~~**Were the index test results interpreted without knowledge of the results of the reference standard?**~~			
11.	**Were the reference standard results interpreted without knowledge of the results of the index test?** (*Was the risk of fracture calculated without the knowledge of the outcome (fracture)?)*	( )	( )	( )
12.	**Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?** *(Is it possible to collect the risk factors included the tool in clinical practice?)*	( )	( )	( )
13.	**Were uninterpretable, indeterminate or intermediate test results reported?** *(Were the any uninterpretable, indeterminate or intermediate results and were the results reported for all patients who were described as having been entered into the study?)*	( )	( )	( )
14.	**Were withdrawals from the study explained?** *(A patient flow diagram or results available for all patients who were reported to have been entered into the study)*	( )	( )	( )
15.	**Were the data on risk factors obtained by clinical interview (as opposed to self-reported)?**	( )	( )	( )
16.	**Were the baseline demographic and clinical features of study participants adequately described?** *(Age, (BMD if measured) and risk factors for fracture included in the tool/tools used in the study (no more than 2 risk factors not reported in baseline description)?)*	( )	( )	( )
17.	***Were all the data needed to calculate the score of the tool/tools available on all subjects?*** *(No missing data on the risk factors included in the tool/tools?)*	( )	( )	( )
18.	**Is the study sample over 1.000 subjects?**	( )	( )	( )
19.	**Did the tool validation study include over 100 events of interest?**	( )	( )	( )
20.	**Was the follow-up period equal to the "recommended" by the tools included in the study?** *(5 or 10 years for all subjects included in the study, depending on the outcome period of the tools)*	( )	( )	( )

Supplementary Table S3. Risk factors included in the fracture risk prediction tools

Tool \ Clinical Risk Factor	Previous fractures	Weight	Age	Smoking	Height	Sex	Parent's fractures or OP	BMD hip (neck)	Previous falls	Glucocorticoids	Alcohol consumption	Rheumatoid arthritis	BMD spine	Secondary causes of OP	Ethnicity	Type II Diabetes	Hormone replacement	Asthma	Cardiovascular disease	Menopausal symptoms	Gastrointestinal disease	Liver disease	Dementia	Chronic disease	Physical activity	Pulse (>80 bpm)	Early menopause	Impaired raise up (activity)	Back pain	Self reported health	Type I Diabetes	Kidney disease	Epilepsy	Parkinson	Living in a nursing home	Anti-depressive drugs	COPD	Cancer	SLE	Anti-convulsive drugs
Computer model for osteoporotic fracture risk																																								
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FRC*																																								
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N=	12	12	11	8	7	6	6	6	5	5	4	4	4	3	3	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

BMD, Bone Mass Index; COPD, Chronic Obstructive Pulmonary Disease; SLE, Systemic Lupus Erythematous; OP, Osteoporosis;
* Updated version of the website, dated Sep. 2014.

Supplementary Table S4. Main characteristics of the studies included in this systematic literature review.

Study	Setting (Country)	Study design and duration of follow-up	Exclusion criteria	Population at baseline (N)	Population available for event verification	% women	Mean age (range)	Number of fractures per site	Fractures ascertainment	AUC
Computer model for osteoporotic fracture risk										
Ettinger (2005) [35]	Gen. Pop. (USA)	Prosp. Cohort 5 yrs	Any described	NA	DM - >400,000 VM-NA	100%	NA (45–79)	Hip, humerus, and wrist- 14,528 Hip – 3,412	NA	NA
FRAMO										
Albertsson (2007) [36]	Gen. Pop. (Sweden)	Prosp. Cohort 2 yrs	NA	1,498	1.248	100%	78.8 yrs (70-100)	Hip-31	GP records	Hip-0.72 Mortality-0.75
Albertsson (2010) [37]	Gen. Pop. (Sweden)	Prosp. Cohort 2 yrs	NA	390	285	100%	79 yrs (72-98)	Hip, distal radius, proximal humerus, pubic bone, ischial bone, vertebrae - 14 Hip-7	Radiographic confirmed	NA
FRAX®										
Kanis (2007) [32]*	Differs with cohort (Several countries)	Prosp. Cohort DM-3,2 yrs VM-NA	Differs with cohort	NA	DM-46,340 VM-230,486	DM - 68% VM-NA	DM - 65 yrs (20-106) VM - 63 yrs (35-116)	DM MOP -3,360 Hip - 850 VM MOP -15,183 Hip – 3,318	Depends on the study	DM With BMD MOP - 0.62 Hip - 0.74 Without BMD MOP -0.60 Hip – 0.66 VM With BMD MOP: - 0.63 Hip – 0.78 Without BMD MOP -0.62 Hip -0.67
Donaldson (2009) [43]*	Post. Menop. (USA)	RCT 3.8yrs	Use of systemic glucocorticoids	3,223	3,043	100%	68.2yrs (55-81)	MOP - 253 Vertebral only - 223	Self reported and radiographic confirmed. Vertebral frc confirmed by Xray	With BMD MOP-0.71 Without BMD MOP -0.68
Ensrud (2009) [44]*	Gen. Pop. (USA)	Prosp. Cohort MOP-8.7 yrs Hip- 9.2 yrs	Black women. Women unable to walk without assistance or with history of bilateral hip replacement	9,704	6,252	100%	71.3yrs (≥ 65)	MOP-1,037 Hip-389	Self reported and radiographic confirmed	With BMD MOP -0.68 Hip -0.75 Without BMD MOP-0.64 Hip-0.71

Leslie (2010) [51]*	OP Screen. (Canada)	Prosp. Cohort NA	None	NA	39,603	92.8%	W 65.7yrs M 68.2yrs (≥50)	MOP-2,543 Hip-549	Radiographic confirmed	With BMD MOP -0.69 Hip -0.83 Without BMD MOP-0.66 Hip-0.79
Sornay-Rendu (2010) [56]	Gen. Pop. (France)	Prosp. Cohort 10yrs	Women with diseases or treatment that affect bone metabolism. HRT use in the last 12 months.	867	867	100%	58.8 yrs (≥ 40)	MOP-82 Hip-17	Self-reported and radiographic confirmed	With BMD MOP -0.78 Without BMD MOP -0.75
Tremollieres (2010) [76]*	Post. Menop. (France)	Prosp. Cohort 13.4yrs	Women treated for osteoporosis > 3 months (with the exception of parathyroid hormone and calcium/vitamin D supplementation.	4,024	2,651	100%	54 yrs (≥ 45)	MOP-145 Hip-13	Self-reported and radiographic confirmed	Without BMD MOP -0.63
Fraser (2011) [46]*	Gen. Pop. (Canada)	Prosp. Cohort 10yrs	Any described	NA	6,697	71.3%	W 65.8 yrs M 65.3yrs (≥50)	MOP: W-12%; M-6.4% Hip: W-2.7%; M-2.4%	Self reported and radiographic confirmed	With BMD MOP -0.69 Hip -0.80 Without BMD MOP-0.66 Hip-0.77
Hillier (2011) [49]	Gen. Pop. (USA)	Prosp. Cohort 9.4yrs	Women unable to walk without assistance and with bilateral hip replacements	7,963	6,252	100%	71 yrs (≥ 65)	MOP- 1,011 Hip-368	Self reported and radiographic confirmed	With BMD MOP (Normal- 0.64; Low bone mass-0.61; Osteoporotic-0.61) Hip (Normal- 0.78; Low bone mass-0.70; Osteoporotic-0.62) Without BMD MOP (Normal- 0.62; Low bone mass-0.59; Osteoporotic-0.61) Hip (Normal- 0.79; Low bone mass- 0.66; Osteoporotic-0.63)
Leslie (2011) [50]	OP Screen. (Canada)	Retr. Cohort 5.5yrs	Available on a different source	NA	36,368	93.1%	65.2 yrs (≥ 50)	MOP-2.321	Confirmed at the discharge diagnostics or hospital.	MOP-0.69 to 0.70
Leslie (2011) [52]	OP Screen. (Canada)	Retr. Cohort DM- 5.5 yrs VM- 5.6 yrs	Available on a different source	NA	37,032	100%	NA (≥ 45)	MOP-1,748	Confirmed at the discharge diagnostics or hospital.	MOP- 0.67 to 0.75
Pressman (2011) [53]*	OP Screen. (USA)	Retr. Cohort 6.6 yrs	Women who did not have at least 1 yr of continuous membership both before and after the DXA scan date, those in whom DXA data were not electronically accessible, and those with missing race/ethnicity and those who had filled a prescription for a bisphosphonate in the year before the DXA test.	NA	94,489	100%	NA (50-85)	Hip-1,579	Confirmed at the discharge diagnostics or hospital.	With BMD Hip -0.84 Without BMD Hip-0.83

Tamaki (2011) [77]	Post. Menop. (Japan)	Prosp. Cohort 10 yrs	Women who did not have femoral neck BMD measurements at the baseline survey, and women taking osteoporosis drugs or HRT at the baseline survey	1,040	815	100%	56.7yrs (40-74)	MOP-43 Hip - 4	Self-reported at each follow-up	With BMD MOP -0.69 Hip -0.88 Without BMD MOP-0.67 Hip-0.86
Cheung (2012) [41]*	Post. Menop. (China)	Prosp. Cohort 4.5 yrs	Women with prescribed osteoporosis treatment	NA	2,266	100%	62.1 yrs (40-90)	MOP- 106 Hip-21	Self-reported and radiographic confirmed	With BMD MOP -0.73 Hip -0.88 Without BMD MOP-0.71 Hip-0.89
González-Macías (2012) [48]*	Gen. Pop. (Spain)	Prosp. Cohort Median 36.1 months	Paget's disease, multiple myeloma, bone metastases, renal failure, hypercalcemia, immobilization for >3 months in the preceding year, anatomical anomalies of the right foot interfering with calcaneal ultrasound measurement, therapeutic doses of fluoride for more than 3 months in the past two yrs or for more than 2 yrs at any time in life, a life expectancy of less than 3 yrs, or participation in any other investigational study involving drugs.	5,146	4,453	100%	72.3 yrs (65–100)	MOP- 201 Hip-50	Self-reported and radiographic confirmed	Without BMD MOP-0.62 Hip-0.64
Ettinger (2013) [45]*	Gen. Pop. (USA)	Prosp. Cohort 8.4 yrs	Men who had used a bisphosphonate within 30 days prior to the baseline visit	5,994	4,291	0%	73.6 yrs (≥ 65)	MOP-374 Hip-161	Self-reported and radiographic confirmed	With BMD MOP-0.67 Hip-0.77 Without BMD MOP-0.63 Hip-0.69
Premaor (2013) [62]	Gen. Pop. (USA)	Prosp. Cohort Obese- 9.1 yrs Non-obese- 9.0 yrs	Women unable to walk without assistance, with bilateral hip replacements and black women	9,704	6,049	100%	NA (≥ 65)	MOP: Obese- 26.9% Non-obese- 32.7%	Self-reported and radiographic confirmed	No additional information provided by authors
Tebe Cordomi (2013) [60]*	OP Screen. (Spain)	Retr. Cohort Median-11 yrs	NA	2,086	1,231	100%	56.8 yrs (40-90)	MOP-222 Hip-13	Self-reported	With BMD MOP-0.61
Azagra (2014) [38]	OP Screen. (Spain)	Prosp. Cohort 10 yrs	Women with wrong number for contact, no responders to 3 calls, treated to osteoporosis ate baseline or during fo-llow up (with exception of supplements). Women died during follow up.	3,247	816	100%	56.8 yrs (40-90)	MOP-49 Hip-15	Confirmed at the GP or hospital.	With BMD MOP-0.74 Without BMD MOP- 0.73
Brennan (2014) [40]	OP Screen. (Canada)	Prosp. Cohort 6.2 yrs	NA	NA	51,327	100%	65.9yrs ≥ 50	MOP- 3723 Hip-1027	Confirmed at the discharge diagnostics or hospital	With BMD MOP- Q1- 0.68 Q5-0.71 Hip- Q1- 0.79 Q5-0.87 Without BMD MOP- Q1- 0.65 Q5-0.68 Hip- Q1- 0.76 Q5-0.85

Friis-Holmberg (2014) [47]*	Gen. Pop. (Denmark)	Prosp. Cohort 4.3 yrs	Participants were excluded if height or weight was missing	18,065	12,758	59.2%	56.8 yrs (40-90)	MOP- 395 Hip-54	Recorded on the GP computer	Without BMD MOP- M- 0.63; W-0.68 Hip- M- 0.76; W-0.86
Sund (2014) [57]*	Post. Menop. (Finland)	Prosp. Cohort 10 yrs	Women who experienced a hip fracture before 1994	13,917	11,182	100%	57.3 yrs (52.4-62.7)	Hip-117	Self-reported and radiographic confirmed	With BMD Hip-0.76 Without BMD Hip- 0.65
FRC										
Lo (2011) [63]	OP Screen. (USA)	Retr. Cohort 6.6 yrs	Women who did not have at least 1 yr of continuous membership both before and after the DXA scan date, those in whom DXA data were not electronically accessible, and those with missing race/ethnicity and those who had filled a prescription for a bisphosphonate in the year before the DXA.	120,972	94,489	100%	62.8 yrs (50-85)	Hip-1,579	Confirmed at the discharge diagnostics or hospital	With BMD Hip-0.85 Without BMD Hip- 0.83
Ettinger (2012) [64]	Gen. Pop. (USA)	Prosp. Cohort 9.2 yrs	Men who had used a bisphosphonate within 30 days prior to the baseline visit	5,994	5,893	0%	73.6 yrs (≥ 65)	MOP-335 Hip-156	Self-reported and radiographic confirmed	With BMD MOP-0.70 Hip-0.79 Without BMD MOP-0.66 Hip-0.71
FRISC										
Tanaka (2010) [59]	Post. Menop. (Japan)	Prosp. Cohort DM-5.3 yrs VM- 10 yrs	DM-Women with metabolic bone disease and secondary osteoporosis	2,187	DM-1,787 VM-400	100%	DM - 63.4 yrs (45-81) VM - 59.5 yrs (41-77)	DM MOP- 383 Immobilization- 83 VM MOP- 60	Available on a different source	VM With BMD MOP- 0.727
FRISC + FRAX®										
Tanaka (2011) [59]	Post. Menop. (Japan)	Prosp. Cohort 5.1 yrs	Women receiving treatment for osteoporosis, and diseases related to secondary osteoporosis	2,010	765	100%	63.3 yrs (NA)	Clinical and morphometric vertebral fractures- 141 Long bone fractures-49	Vertebral fractures were evaluated using radiographs taken at baseline and during the follow-up. No reference to the other types of fractures	Vertebral frt: FRAX® 0.690, FRISC 0.702, Pentosidine+FRISC 0.732. Vertebral frt and long bone frt: FRAX® 0.671, FRISC 0.685
FRISK										
Henry (2006) [66]	Gen. Pop. (Australia)	Cros. Cohort 2.0 yrs	NA	NA	Cases-231 Control-448	100%	Cases-74 yrs Control-72 yrs (≥60)	NA	Radiology reports	NA

Henry (2011) [67]	Gen. Pop. (Australia)	Prosp. Cohort Median-9.6 yrs	NA	600	600	100%	Median-74 yrs (≥50)	MOP-125 Hip-34	Radiology reports	With BMD MOP-0.66 Without BMD MOP-0.62
GARVAN										
Nguyen (2007) [34]	Gen. Pop. (Australia)	Prosp. Cohort Median-13 yrs	NA	3,676	1,768	58%	NA ≥ 60	Hip: W-96, M-31	Radiology reports	DM - With BMD Hip- W-0.85; M - 0.85
Nguyen (2008) [69]*	Gen. Pop. (Australia)	Prosp. Cohort W median 13 yrs; M median 12 yrs	NA	3,676	2,396	56.7%	W 71 yrs M 70 yrs (≥ 60)	MOP: W-426; M-149	Radiology reports	With BMD MOP W- 0.757; M - 0.754
Langsetm (2011) [68]*	Gen. Pop. (Canada)	Prosp. Cohort 8.6 yrs	NA	9,423	5,758	72.1%	68 yrs (55-95)	MOP: W-583; M-116	Self report annually and 78% Radiographic confirmed	With BMD MOP: W0.69; M- 0.70 Hip W-0.80; M- 0.85
GARVAN + FRAX®										
Sandhu (2010) [55]	OP Screen. (Australia)	Retr. Cohort Fct-1.7 yrs No Fct-3.7 yrs	If any prior MOP fracture, any treatment with bone-specific agent for > 30 months, or presence of metabolic bone disorder	530	200	72%	W Fct -73 yrs W No Fct -68 yrs M Fct- 75 yrs M No Fct – 68 yrs (60-90)	MOP FRAX® W-69 MOP FRAX® M-31	Medical records	**FRAX®-US** MOP: W- 0.77;0.54 **FRAX®-UK** MOP: W-0.78; M-0.57 **GARVAN** MOP: W-0.84; M-0.76
Bolland (2011) [39]*	Post. Menop. (New Zealand)	Prosp. Cohort 8.8 yrs	Women with major medical conditions, and if they were taking treatment for OP (including HRT or vitamin D supplements in doses > 1000 IU/day and had serum 25(OH)D levels ≥25 nmol/L. Not have a measurement of femoral neck BMD at baseline	1,471	1,422	100%	74.2 yrs (≥ 55)	MOP FRAX®- 16% MOP GARVAN-19.6% Hip- 4%	Self report	**FRAX** With BMD MOP-0.64 Hip-0.70 Without BMD MOP-0.62 Hip-0.69 **GARVAN** With BMD MOP-0.64 Hip-0.67
Sambrook (2011) [54]	Gen. Pop. (10 countries)	Prosp. Cohort 2 yrs	Women were excluded if they were unable to complete the study survey owing to cognitive impairment, language barriers, institutionalization, or illness, aged younger than 60 years, those on antiosteoporotic medication, and those with incomplete data	60,393	19,586	100%	NA (≥ 60)	MOP FRAX®- 468 MOP GARVAN- 538 Hip- 69	Self-reported	**FRAX®:** Without BMD MOP-0.60 Hip-0.65 **GARVAN** Without BMD MOP-0.64 Hip-0.61

QFracture®										
Hippisley-Cox (2009) [33]*	Gen. Pop. (England and Wales)	Prosp. Cohort DM- 7,898,208 person yrs VM- 4,401,261 person yrs	Patients with no previous recorded fracture, temporary residents, and patients with interrupted periods of registration with the practice and patients who did not have a valid Townsend deprivation score.	DM- 2,391,756 VM- 1,294,732	DM- 2,357,895 VM-1,275,917	DM- 50.2% VM- 50.3%	DM - Median W 48 yrs M 46 yrs VM - Median W 49 yrs M 46 yrs (30-85)	DM MOP-32,284 Hip- 12,369 VM MOP-18,471 Hip- 7,162	Recorded on the GP computer records	VM MOP: W- 0.79; M-0.69 Hip: W- 0.89; M- 0.86
Collins (2011) [70]*	Gen. Pop. (UK)	Prosp. Cohort Median MOP -5.98 yrs Hip - 6.03 yrs	Patients with no previously recorded fracture (hip, distal radius, or vertebra), temporary residents, and had no interrupted periods of registration with a practice	2,244,636	2,209,451	50.6%	Median W 48 yrs M 47 yrs (30-85)	MOP-25,208 Hip- 12,188	Recorded on the GP computer records	MOP: W- 0.82; M-0.74 Hip: W-0.89; M-0.86
Updated QFracture® (2012)										
Hippisley-Cox (2012) [71]*	Gen. Pop. (UK)	Prosp. Cohort DM- 23,608,337 person yrs, VM- 11,732,106 person yrs	Any described	NA	DM- 3,142,673 VM- 1,583,373	DM- 50.9% VM- 49.2%	DM - 50 yrs VM - 50 yrs (30-100)	DM MOP- 59,772 Hip-20,028 VM MOP- 28,685 Hip- 9,610	Recorded on the GP computer records	VM MOP: W- 0.79; M- 0.71 Hip: W- 0.89; M- 0.88
QFracture®+FRAX®										
Cummins (2011) [42]*	OP Screen. (UK and Ireland)	Retr. Cohort NA	Subjects who were receiving treatment for osteoporosis, those on corticosteroids, and those with a secondary cause of osteoporosis such as malabsorption, chronic liver disease, renal failure, and malignant disease	NA	Cases-246 Controls-338	100%	Fct - 68 yrs Ctl – 66 yrs (50-85)	MOP-246	NA	**FRAX®** Without BMD MOP W- 0.67 HIP W - 0.71 **QFracture®** MOP W 0.67 HIP W- 0.64
Score for estimating the long-term risk of fracture in post menopausal women										
Van Staa (2006) [72]	OP Screen. (UK)	Prosp. Cohort DM-5.8 yrs VM-5.6 yrs	Women with recent use of oral glucocorticoids.	NA	DM- 366,104 VM- 32,728	100%	NA (≥ 50)	MOP-14,011 Clinical vertebral-1,610 Hip-6,453	Recorded on the GP computer records	DM MOP - 0.60 Hip - 0.84 Clinical vertebral - 0.69 VM NA
Simplified fracture risk system										
Leslie (2009) [73]	OP Screen. (Canada)	Retr. Cohort 3.1 yrs	NA	NA	16,205	100%	65 (≥ 50)	NA	NA	No AUC
SOF										
Ahmed (2006) [74]	Gen. Pop. (Norway)	Prosp. Cohort Max-5 yrs	History of previous hip fracture	5,795	1,410	100%	No Hip- 69.5 yrs Hip-70.4 yrs (65-84)	All non-vertebral Fct- 170 Hip-49	Hospital codes discharge	No AUC

WHI										
Hundrup (2010) [75]	Post. Menop. (Denmark)	Prosp. Cohort 5 yrs	Premenopausal women with: 50<age<79 yrs; 42<weight <162 kg; 140<height<179 cm. If they had missing items in the questionnaire on smoking status, physical activity and self-reported health.	15,648	13,353	100%	61 yrs (≥ 45)	Hip-122	Recorded on the national register records	Hip-0.82

AUC, Area Under the Curve; CI, Confidence Interval; Cros. Cohort, Cross-sectional Cohort; Ctl, Control; DM, Derivation model; Frt, Fracture; Gen. Pop., General Population; GP – General Practitioner; HRT, Hormone Replacement Therapy; M, Man; MOP, Major Osteoporotic Fracture; NA, Not available; Post. Menop., Post Menopausal; Prosp. Cohort, Prospective Cohort; Retr. Cohort, Retrospective Cohort; OP Screen., Osteoporosis Screening; VM, Validation model; W, Women; yrs, Years.
* Included in Meta-analysis.

Supplementary Table S5. Articles excluded from the meta-analysis. All studies with FRAX®.

Article	Reason of exclusion
Sornay-Rendu (2010) [55]	Number of fractures <100
Hillier (2011) [48]	Authors only provide AUC values for specific subgroups accordingly to specific objectives of the study (different BMD categories).
Leslie (2011) [49]	The AUC values were provided regarding specific objectives of study (Use of T-score of lumbar spine or femoral neck)
Leslie (2011) [51]	The AUC values were provided regarding specific objectives of study (Use of T-score of lumbar spine or femoral neck)
Tamaki (2011) [84]	Number of fractures <100
Premaor (2013) [61]	No additional information provided by authors
Azagra (2014) [37]	Number of fractures <100
Brennan (2014) [39]	Authors only provide AUC values for specific subgroups accordingly to specific objectives of the study (different socioeconomic status).
Sambrook (2011) [53]	No additional information provided by authors
Sandhu (2010) [54]	FRAX® model not validated for the country; Number of fractures <100

AUC, Area Under the Curve; BMD, Bone Mass Density.

Supplementary Figures S1 and S2– *Methodological quality of the studies with QUADAS-2.*

According to our assessment with QUADAS-2 (Figure S1), the average quality of 45 studies was higher in item 12 - similarities between data available during study interpretation and clinical practice; item 2 - description of the selection criteria; and items 8 and 9 - provision of sufficient details to allow replication. However, many studies did not report enough data to analyse the accuracy of the tools at the end of study (item 17) or at interim/intermediate analysis (item 13). The reasons for withdrawal are also lacking in many articles (item 14). The number of participants lost during the follow up due to death is conspicuously missing in most studies. Adherence to the recommended time of follow-up for the used tool (item 20) was only present in 16 studies.

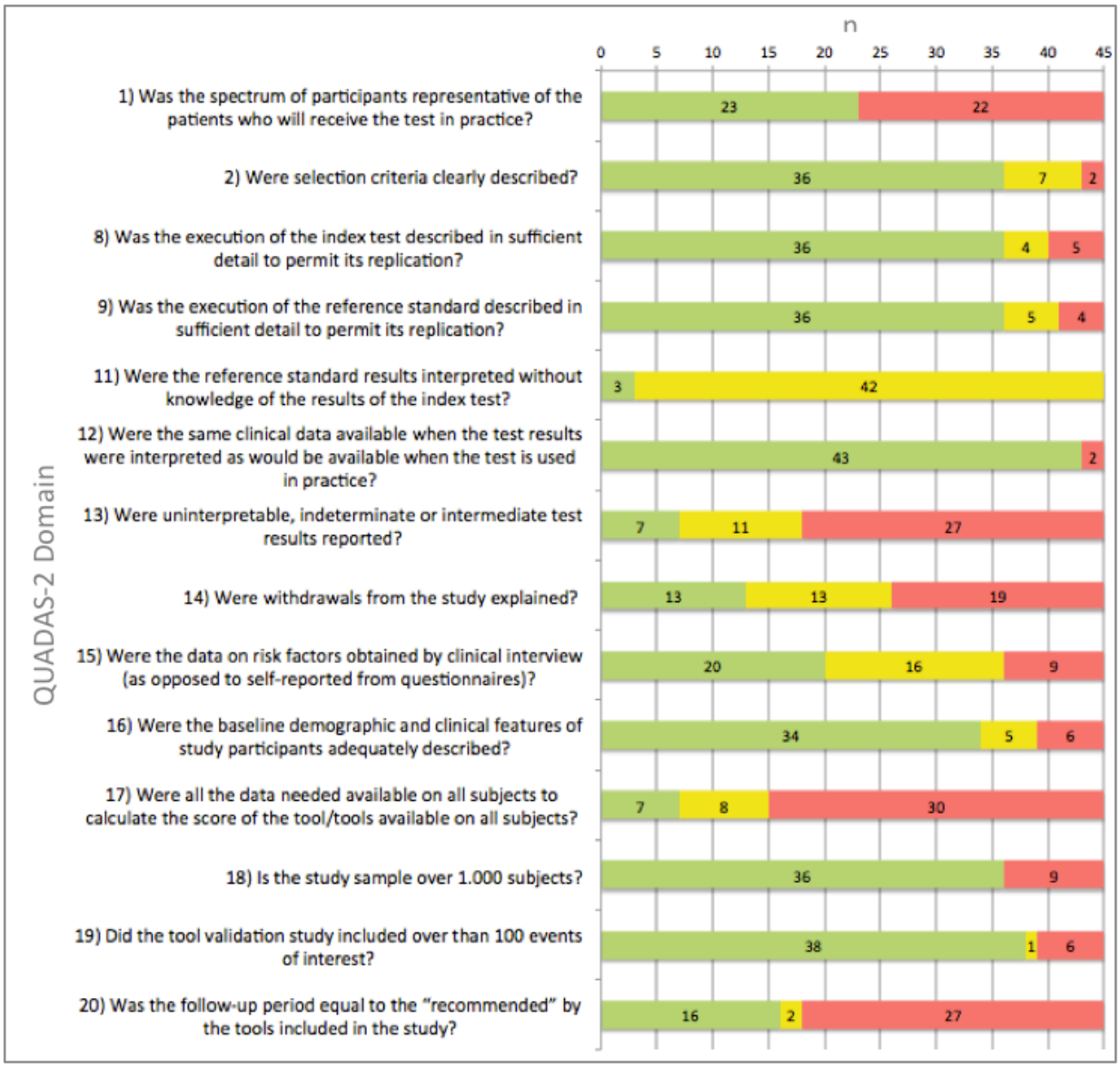

Figure S1 – Quality assessment of studies testing fracture risk prediction tools (n=45).

Green= Yes; Yellow=unclear; Red= No.

We also compared the quality of reports dealing with the 3 most developed tools (Figure S2). Articles on FRAX® performed better than average on items 11 and 13, while GARVAN's articles performed better on items 2, 8, 9, 14, 16, 17 and 20 and QFracture® studies on items 1, 2, 15 and 19.

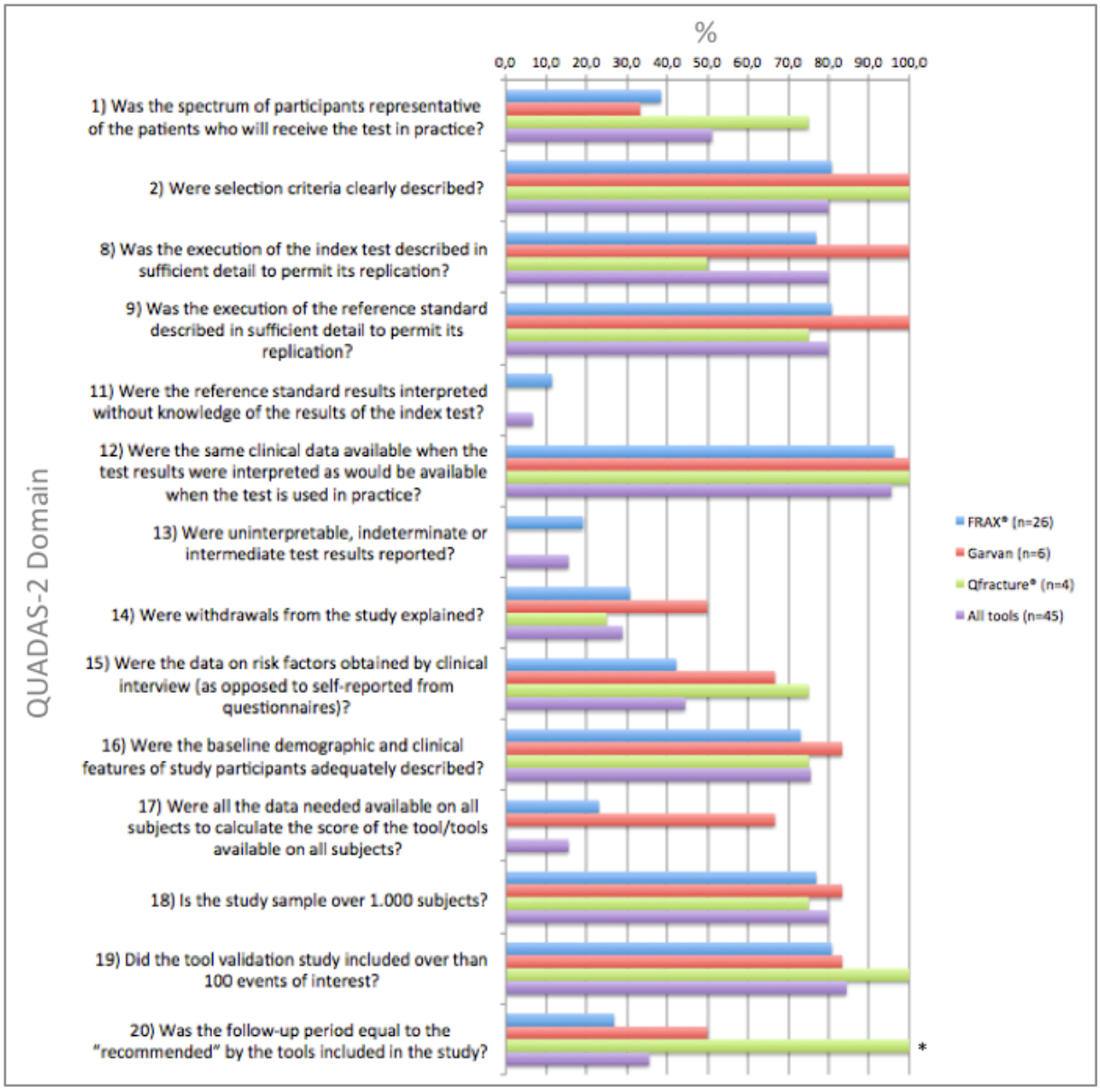

Figure S2. Percentage of articles complying with quality criteria, according to risk prediction tool under evaluation.

* QFracture® has only been validated for the 10-years prediction interval.

Chapter 3

A FRAX® MODEL FOR THE ESTIMATION OF OSTEOPOROTIC FRACTURE PROBABILITY IN PORTUGAL

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Marques A, Mota A, Canhão H, Romeu J, Machado P, Ruano A, Barbosa A, Aroso A, Silva D, Araújo D, Simões E, Águas F, Rosendo I, Silva I, Crespo J, Alves J, Costa L, Mascarenhas M, Lourenço O, Ferreira P, Lucas R, Roque R, Branco J, Tavares V, Johansson H, Kanis J, da Silva JAP.

A FRAX® model for the estimation of osteoporotic fracture probability in Portugal.

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ABSTRACT

Introduction

The objective of this study was to develop a Portuguese version of the World Health Organization fracture risk assessment tool (FRAX®).

Methods

All cases of hip fracture occurred at or after 40 years of age were extracted from the Portuguese National Hospital Discharge Register from 2006 to 2010. Age and sex-ranked population estimates and mortality rates were obtained from National Statistics. Age- and gender stratified incidences were computed and the average of the five years under consideration was taken. Rates for other major fractures were imputed from the epidemiology of Sweden, as undertaken for most national FRAX® models. All methodological aspects and results were submitted to critical appraisal by a wide panel of national experts and representatives of the different stakeholders, including patients.

Results

Hip fracture incidence rates were higher in women than in men and increased with age. The lowest incidence was observed in 40-44 years group (14.1 and 4.0 per 100,000 inhabitants for men and women, respectively). The highest rate was observed among the 95-100 age-group (2,577.6 and 3,551.8/100,000 inhabitants, for men and women, respectively). The estimated 10-year probability for major osteoporotic fracture or hip fracture increased with decreasing T-score and with increasing age.

Conclusions

Portugal has one of the lowest fracture incidences among European countries. The FRAX® tool has been successfully calibrated to the Portuguese population, and can now be used to estimate the 10-year risk of osteoporotic fractures in this country. All major stakeholders officially endorsed the Portuguese FRAX® model and co-authored this paper.

INTRODUCTION

Osteoporosis is a serious worldwide epidemic. In the year 2000 around 9.0 million osteoporotic fractures occurred of which 1.6 million were at the hip, 1.7 million at the forearm and 1.4 million were clinical vertebral fractures.[1] It is estimated that 8000 to 10,000 osteoporotic hip fractures occur in Portugal each year.[2 3] According to the available data it is estimated that 10 to 20% of these patients die within one year and 50% become unable to walk without support and therefore institutionalized or dependent on others for simple personal care.[3] Over and above this should be added the morbidity and mortality from osteoporotic fractures at other sites (spine, forearm, humerus, ribs).[4] This extraordinary burden underlines the importance of identifying individuals and populations at higher risk of fracture so that preventive measures can be targeted effectively.

With this purpose, the World Health Organization (WHO) developed a fracture risk assessment tool, named FRAX.[5] FRAX® is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that provides an estimate of fracture probability in men and women over the subsequent ten years, based on clinical risk factors (CRFs) with or without the inclusion of bone mineral density (BMD) measured at the femoral neck.[5 6] The identification of the significant CRFs for osteoporotic fracture was supported by a series of meta-analyses. Data from 9 prospective primary cohorts were analysed and the results were validated in 11 other prospective cohorts. These cohorts included more than 275,000 persons corresponding to 1.4 million person-years with more than 22,711 reported fractures.[7] Clinical risk factors identified as relevant included, a prior fragility fracture,[8] age and sex,[9] body mass index,[10] prior use of glucocorticoids,[11] secondary osteoporosis,[12] rheumatoid arthritis,[12] a parental history of hip fracture,[13] current cigarette smoking,[14] and alcohol intake of 3 or more units/day.[15] The FRAX tool provides a 10-year probability estimate for osteoporotic hip fracture and for major osteoporotic fractures. The latter metric represents a composite of hip, clinical spine, proximal humerus and forearm fractures. The probability estimate takes account of, not only the fracture risk, but also the risk of death in a given individual.[6]

Since osteoporotic fracture rates vary greatly between countries, the FRAX algorithm is calibrated to the target population.[16] A total of 50 country and/or ethnic models are currently available[17] and several others are being developed. The relative impact of the various clinical risk factors included in FRAX is assumed to be similar in different countries.[18]

Ideally, the country-specific calibration of osteoporotic fracture rates would be based on country-specific incidence data for hip and for each of the other osteoporotic fractures that are considered. However, it is not usually possible to obtain accurate data on non–hip fractures, because many of these do not result in hospitalization or do not require surgery,

and so escape to the national hospital discharge registries. This difficulty, common to most countries, has been overcome by imputing non–hip fracture rates based on the gender- and age-specific ratio of hip to non–hip fractures observed in a prospective population-based study performed in Malmo, Sweden.[10 19] This imputation method has been used in the development of several FRAX models[5] and appears to be valid for West European countries, Australia and USA.[20]

The aim of the present study was to describe the epidemiology of osteoporotic hip fractures in the Portuguese population and its application to the development of the Portuguese FRAX model. We discuss the underlying assumptions and limitations of this model and present the process that allowed its nation-wide endorsement.

METHODS

Steering Committee

This project was funded by the Portuguese Government through the *Direcção Geral da Saúde* – DGS (Portuguese Health Directorate) after a proposal presented by *Associação Nacional Contra a Osteoporose* – APOROS (National Association Against Osteoporosis) and by an unrestricted grant from Amgen. The principal investigator (JAPS) invited a number of national experts on osteoporosis and representatives of all the relevant Portuguese scientific societies and patient associations to form a Steering Committee, the role of which was to discuss and decide by consensus or majority vote on all relevant aspects of the methodology and results and to seek official endorsement from their organizations to the final model. This work was done through three rounds of e-mail communication and a formal meeting. This paper represents the final consensus endorsed by all individuals and societies involved. The data were collected and analysed by a research nurse (A Marques) with the assistance of an expert in our national discharge registry (A Mota). The organizations and individual experts represented in the panel are given in the authors' affiliation list.

Data sources, time span and geographical area

For the calibration of FRAX, we used two different sources of data: (1) the National Hospital Discharge Register maintained by the *Administração Central dos Serviços de Saúde* - ACSS (Central Administration of Health Service) and (2) the national resident population and mortality statistics, provided by the *Instituto Nacional de Estatística* – INE (Portuguese Statistics Institute).

The National Hospital Discharge Register provides high quality information and the ACSS, responsible for its maintenance, guarantees that over 99% of all hospital admissions are

registered by properly trained medical staff. The database is submitted to regular quality checks which have met international quality standards at European and global levels for at least ten years. For the purpose of this report, the steering panel decided to include data for the 5 years from 2006 to 2010.

The same quality standards are not provided in the Madeira and Azores autonomous regions, since the accuracy of the register cannot be audited. According to INE, Madeira and Azores had 493,379 inhabitants compared to 10,636,979 in mainland Portugal in 2010. The steering panel decided, therefore, to exclude data from these regions and to limit the analysis to mainland Portugal.

The Portuguese National Hospital Discharge Register does not report admissions to emergency care without hospitalization. This led the steering committee to consider that data from the registry on non-hip osteoporotic fractures were not reliable, as most of these fractures do not require hospitalization. The panel recognized that it would be impossible to obtain reliable data on those fractures and thus accepted that the imputation from Malmo would be applied as previously described.[6]

The Portuguese National Hospital Discharge Register is limited to the National Health Service and does not include admissions to private hospitals. There are no statistics related to these hospitals. In Portugal, access to the national health-care service is universal and almost free of charge for all the population from all social groups and all ages. Private hospitals have only recently gained significant usage and the panel estimated that, due to the high costs involved, only a small minority of osteoporotic hip fractures would have been treated outside public hospitals, thus escaping the database we used. By majority vote, the panel decided that the National Hospital Discharge Register was a valid representation of the epidemiology of osteoporotic hip fractures for the Portuguese mainland population.

The annual age and sex distribution of the Portuguese population was provided by the Portuguese INE (http://www.ine.pt) up until the age of 85 years. For age groups above 85 years, population data was calculated from The Human Mortality Database (http://www.mortality.org) provided by the same Institute.

Mortality data were obtained from Portuguese Instituto Nacional de Estatística (http://www.ine.pt) for the years 2006 to 2010.

Fractures included

The Portuguese National Hospital Discharge Register uses the ICD-9-CM for coding and this has remained the same over the time interval under study. We transposed the codes requested by WHO in ICD-10 to ICD-9. The correspondence was submitted to consensus with experts in coding and in Orthopaedics within the steering panel. Using the electronic

National Registry of Hospitalized Persons containing patient hospital discharge notes, all patients were identified with the corresponding ICD-9 codes of proximal femur fracture: 820.02, 820.03, 820.08, 820.09, 820.10, 820.11, 820.12, 820.13, 820.21, 820.31 (ICD10: S72.0 femoral neck fracture), 820.22, 820.32 (ICD10: S72.1 pertrochanteric fracture), and 820.22, 820.32 (ICD10: S72.2 subtrochanteric fracture). By a majority vote, we did not exclude high-energy fractures, even though our register would allow these to be identified since the frequency of fractures following high energy trauma was higher in patients with osteoporosis than those without osteoporosis.[21] The number of hip fractures under the above mentioned codes reportedly associated with high-energy trauma represented 2.3% of all hip fractures over the 5 years under study. Fractures associated with malignancy and repeat admissions of same patient for a similar fracture within the period under study were excluded.

Calculation of fracture incidence rates

The rates of hospitalization for hip fracture for each gender and age-group (5-year intervals) above 40 years of age, were computed for each calendar year from the number of hospital admissions and resident population, and expressed as cases per 100,000. There was no age-specific time trend in incidence seen from 2006 to 2010 (p=0.24) in men (HR= 0.96; 95% confidence interval = 0.85-1.09) or women (HR=1.04; 95% CI= 0.97-1.12). For this reason, the annual incidence for the five-year period was calculated as the mean of the five yearly incidence rates for each age group and gender. Similar calculations were done for mortality.

Calibration

The development and validation of FRAX have been extensively described.[6 20 22] The computation of fracture probability integrates the risk of death and the risk of fracture and takes into account several clinical risk factors with demonstrated effects on the fracture hazard and, where found, the risk of death. Calculations can be performed with or without the inclusion of BMD at the femoral neck.

Poisson models were used to calculate the hazard functions of fracture and death. Age-and gender-specific fracture and mortality hazards were computed. The relationship between the hazard functions was used to calculate the 10-year probability of fracture for a combination of given risk factors.[4 18] The independent contribution of each risk factor was used to compute probabilities of fracture in the absence of clinical risk factors or in the presence of any combination.[5]

The relative impact of each clinical risk factor and T-score is assumed to be the same in all populations. Therefore, risks estimated by different country-specific FRAX® models should have a similar impact of all clinical risk factors, the differences being a translation solely of

the background incidence of fracture and the mortality of the index population. The Steering Panel accepted this assumption, but advised that its validity should be evaluated in our population.

RESULTS

The age (5 year age intervals) and gender-specific annual incidence rates for hip fracture in the Portuguese population are presented in Table 1. The rate of hip fractures was very consistent over the five-year interval under appreciation, as demonstrated by the small range around the average. Hip fracture rates in men and women showed a similar age-dependent increase. Hip fractures were rare prior to age 65 years but then increased sharply in both sexes. Men had higher hip fracture rates than women prior to age 59 years, after which women had substantially higher hip fracture incidences. Mortality rates (Table 1) showed, as expected, an increase with age. Men had higher age-specific mortality than women across the age spectrum.

Data presented in Table 1 was used to calibrate the Portuguese version of FRAX. An example of the integration of these hazards is shown in Table 2 which shows the effect of BMD on the 10-year probabilities of major osteoporotic and hip fracture in Portuguese men and women aged 75 years with a BMI of 24 kg/m^2 and a parental history of hip fracture. Fracture risk estimates increased with decreasing T-score. At any given BMD, women had a higher 10-year probability of major osteoporotic fracture than men. The 10-year probability of hip fracture was higher in women than in men with these clinical risk factors, except for a T-score equal or higher than -1 SD, when the reverse was observed.

Table 1. Age- and gender-specific hip fracture incidences and mortality in the Portuguese mainland population.

Age category (years)	Average annual hip fracture incidence per 100,000 inhabitants, 2006-2010 (range)		Average annual mortality rate per 100,000 inhabitants, 2006-2010.	
	Male	Female	Male	Female
40-44	14.1 (12.2-14.9)	4.0 (3.2-5.3)	278	113.0
45-49	18.4 (15.4-21.4)	6.9 (6.3-7.7)	416	171.0
50-54	22.3 (19.5-25.7)	15.4 (14.7-16.3)	608	239.8
55-59	31.6 (26.8-34.1)	29.6 (27.3-33.2)	822	338.6
60-64	45.1 (37.6-48.8)	60.6 (57.3-63.1)	1,192	504.6
65-69	75.9 (67.3-81.3)	117 (110-128)	1,819	829.0
70-74	129 (122-134)	274 (270-281)	2,983	1,507.0
75-79	264 (238-281)	609 (572-625)	5,148	2,913.2
80-84	535 (502-570)	1,190 (1147-1218)	9,279	6,080.2
85-89	1,006 (900-1099)	2,291 (1997-2495)	13,217	11,098
90-94	1,663 (1502-1772)	2,989 (2704-3395)	17,422	16,206
95-99	2,578 (2310- 2938)	3,552 (3198-3958)	19,452	19,101

Numbers represent the average of the five annual incidences calculated for each year of the time interval 2006-2010. Numbers in brackets represent the minimum and maximum annual incidences for each age-group and gender in individual calendar years from 2006-2010.

Table 2. Estimated 10-year probability (%) of major osteoporotic and hip fracture for a 75-year-old Portuguese man or woman with a BMI of 24 kg/m^2 and a parental history of hip fracture according to the T-score of femoral neck BMD.

T-Score	Men		Women	
	Major osteoporotic fracture	Hip fracture	Major osteoporotic fracture	Hip fracture
Not taken into account	9.7	7.0	19	13
1	3.5	1.4	4.8	0.9
0	5.1	2.7	6.8	2.2
-1	7.9	5.3	10	5
-2	14	11	17	11
-3	23	20	32	25
-4	38	35	55	49

Data from www.shef.ac.uk/frax

Table 3, shows the 10-year probabilities of osteoporotic fractures for Portuguese men and women by age and gender in the absence or presence of at least one single clinical risk factor, when BMD information is not available and with a constant BMI of 24 kg/m^2. At younger ages, the differences between the two genders were smaller. For example the 10-

year probability of osteoporotic fracture was estimated at 1.6% in a 50-year-old female with a BMI of 24 kg/m^2 and with current smoking as the single clinical risk factor, as compared to 1.3% in a 50-year-old male with a similar clinical risk factor. In the elderly, the differences were larger with the same scenarios but for a woman aged 90 years the 10-year probability of osteoporotic fracture was 18% against 8.4% for 90-year old man. Parental history of hip fracture was the strongest clinical risk factor in the elderly: a 90-year-old woman with a BMI of 24 kg/m^2, and a parental hip fracture as single clinical risk factor, had a 34% 10-year probability of osteoporotic fracture, whilst the risk was only 17% for a female of equal age and BMI without a parental hip fracture.

Table 3. 10-year probabilities (%) of osteoporotic fracture in absence or presence of each clinical risk factor, without information on BMD by age (years (y)) and sex (BMI set at 24kg/m^2)

Clinical risk factor	Men					Women				
	50y	60y	70y	80y	90y	50y	60y	70y	80y	90y
No risk factor	1.2	1.8	3.3	6.5	7.9	1.5	2.8	6.4	15	17
Previous fracture	2.6	3.8	6.4	11	12	3.4	5.9	12	23	27
Parental hip fracture	2.4	3.4	5.5	14	19	3.0	5.3	11	29	34
Current smoking	1.3	1.9	3.6	7.0	8.4	1.6	3.1	7.3	16	18
Glucocorticoid use [a]	2.0	2.9	5.1	9.4	11	2.5	4.7	11	22	24
Rheumatoid arthritis	1.6	2.5	4.8	9.9	12	2.1	3.9	9.3	21	25
Secondary osteoporosis [b]	1.6	2.5	4.8	9.9	12	2.1	3.9	9.3	21	25
Alcohol use [c]	1.5	2.2	4.2	8.7	11	1.9	3.5	8.2	19	23

[a] Current exposure to oral glucocorticoids or prior exposure for a period of at least 3 months at a daily dose of at least 5 mg prednisolone (or equivalent doses of other glucocorticoids). [b] Includes patients diagnosed with diabetes mellitus type I, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption, and chronic liver disease. [c] Exposure to at least three units of alcohol daily (one unit equals 8–10 g alcohol).
Data from www.shef.ac.uk/frax

Table 4 shows fracture risk estimates for males and females at 3 different ages at a T score of -2.5 SD and a BMI of 24 kg/m^2 for men and women from Portugal and other selected European countries. Ten-year probability estimates for hip and a major osteoporotic fracture for Portugal are slightly higher than for Spain and lower than for Italy but substantially lower than probabilities in the United Kingdom and particularly in Sweden.

Table 4. Estimated 10-year risk estimates of hip and a major osteoporotic fractures (%) in men and women aged 65, 75, and 85 years (y) at the threshold for osteoporosis (T-score = –2.5 SD), with no clinical risk factors, in selected European countries (BMI set at 24 kg/m^2)

Country	Men						Women					
	Hip Fracture			Major osteoporotic fracture			Hip Fracture			Major osteoporotic fracture		
	65y	75y	85y	65y	75y	85y	65y	75y	85y	65y	75y	85y
Portugal	2.4	3.7	4.3	5.0	7.2	7.7	2.1	4.2	6.2	6.0	11.0	14.0
Spain	2.0	3.4	3.7	4.5	6.3	7.1	1.7	3.9	5.3	5.4	9.3	13.0
Italy	3.5	5.0	5.7	7.5	9.5	10.0	2.9	5.5	7.6	8.6	14.0	17.0
UK	3.4	4.0	4.4	9.3	9.1	8.4	2.9	4.8	7.7	12.0	15.0	18.0
Sweden	5.9	8.7	7.3	13.0	15.0	13.0	4.8	9.3	10.0	15.0	21.0	23.0

Data from www.shef.ac.uk/frax

DISCUSSION

This article, describes the FRAX® model developed for Portugal, which can be used to assess individual 10-year probabilities of hip fracture, as well as of osteoporotic fracture in Portuguese men and women. It has been calibrated to the total population of mainland Portugal, based on nationwide incidence rates for hip fracture and mortality (data 2006-2010) according to the procedure established by the WHO Collaborating Centre.

The methodology employed to establish the national incidence of hip fractures is robust and the results are very stable across the years under consideration and their pattern by age and sex consistent with current knowledge on the epidemiology of hip fractures around the world (Table 1). These data suggest that ICD coding in the national database was accurate. However we can see higher incidence of hip fractures in males compared to females in the age category 40-59 year. One of the contributions to this finding lies in the inclusion of high-energy fractures. These fractures only represented 2.3% of all hip fractures, and the same methodology has been employed in other national validations of FRAX® with similar findings.[23-25] However, this must be acknowledged as a limitation of FRAX®-Port.

Portugal presents one of the lowest incidences of hip fracture in Europe, very similar to that observed in Spain. This will, obviously, translate into lower 10-year probabilities estimated by FRAX®. Apart from hip fracture, most osteoporotic fractures in Portugal are managed in emergency rooms and are not entered into any form of national registry. For this reason, the estimation of major osteoporotic fracture is supported, in our model, on extrapolations from actual data collected in carefully followed up cohorts. This technique has been used in most national models of FRAX® and assumes that the ratio of hip/major osteoporotic fractures is similar to that observed in Sweden and similarly affected by certain epidemiological factors

such as age and gender.

The incorporation of this FRAX® model into daily clinical practice and clinical guidelines for the management of osteoporosis can now be considered in Portugal, as in other countries.[17]

Users are advised to take into account the strengths and limitations of FRAX® which have been extensively discussed.[26 27] FRAX® should not be seen as a precise instrument or a gold standard for patient management, but rather as a reference platform exposed to critical appraisal according to specific patient features.[28]

The strengths of the FRAX® tool are many and valuable: this is a model based on extensive data from multiple cohorts with and without BMD, which has been extensively validated in additional cohorts.[5] It is adapted to each country, by incorporating the local epidemiology of fracture and mortality. Finally, it is easy to access and applicable to men (aged 50+ years) as well as to postmenopausal women. The FRAX® model may also facilitate the communication between patient and clinician in weighing the risks and benefits of starting fracture prevention.

Obviously, the FRAX® models may need to be updated from time to time to take account of changing epidemiology and population structure. We are planning to do this if any substantial difference becomes apparent in the Portuguese census 2011, when these data become available.

Some authors criticise FRAX® in general for not making use of several important clinical risk factors for fracture. This limitation is due either to the lack of valid data to incorporate that factor in the model (e.g. history of falls) or because of difficulties in their accurate quantitation in a primary care setting (physical activity, vitamin D deficiency, bone turnover markers, or loss of bone mass between sequential BMD measurements).[9 26 29-33] Also, FRAX® does not take into account characteristics of prior fractures such as their number and severity.

FRAX® Portugal was not validated for ethnic minorities living in our country. In such cases we can only recommended that the health care practitioner uses good clinical judgment, in that ethnic minorities in Portugal (e.g. Asians and Blacks) will likely have a lower fracture risk as seen in other countries.[18 34] Conversely, it is probable that the incorporation of data from minorities into the National model will not significantly affect the estimations for the Portuguese Caucasian population as this segment of the population is largely predominant: according to data provided by Portuguese National Institute of Statistics (http://www.ine.pt) in 2008, there were 124,291 individuals born in Africa and 27,814 individuals born in Asia living (legally) in Portugal, representing 1,5% of the total population. Two countries have constructed ethnic specific FRAX models for their ethnic minorities: USA and Singapore.[28]

FRAX®-Port has not been prospectively validated in Portugal. This is a difficult task, which

requires careful data collection in large numbers of people that are representative of the general population. Several studies are in progress in Coimbra (SAOL[35-37]), Oporto,[38] and other Portuguese prospective cohorts.

The use of FRAX® as a clinical tool demands a consideration of intervention thresholds. These should be based on clinical imperatives and consider the cost-effectiveness of possible FRAX®-based strategies in the epidemiological, social and economic context of each country,[6 39-42] Studies on the health and economic impact of different intervention thresholds in Portugal are also underway.

In conclusion, a FRAX® tool has been developed to compute fracture probabilities calibrated to the epidemiology of Portugal. The FRAX® tool is a major advance in the management of osteoporosis in both postmenopausal women and men aged above 50 years, allowing a multidimensional estimate of the 10-year probability of osteoporotic fracture and, thus, the tailoring of pharmacological interventions to high-risk subjects.

Further studies are necessary to assess the validity of predictions offered by FRAX®-Port in our population and propose any appropriate adjustments regarding the impact of specific risk factors. Research is also needed at a national level to establish the cost-effectiveness of possible FRAX®-based prevention and intervention strategies.

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Chapter 4

FRACTURE RISK PREDICTION USING CLINICAL RISK FACTORS AND BMD: PERFORMANCE OF THE FRAX® TOOL IN THE GENERAL POPULATION, DOES NOT IMPROVE WHEN BMD IS ADDED.

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Marques A, Lucas R, Simões E, Jacobs J, da Silva JA. Fracture risk prediction using clinical risk factors and BMD: performance of the FRAX® tool in the general population, does not improve when BMD is added. Submitted to Osteoporos Int

ABSTRACT

Introduction

A recent systematic review of the literature highlighted a number of relevant limitations in the previous studies assessing the performance of FRAX® in estimating the risk of fractures over 10-years.

Methods

We investigated FRAX® discrimination and calibration in a prospective multicenter study of the general population, according to the STROBE statement for cohort studies. Participants aged ≥40 years were identified from 3 Portuguese cohorts (n=2626), through 1999-2014. Ten-year fracture probabilities were calculated using baseline data applied to the Portuguese version of FRAX®, with and without BMD. Performance was assessed through discrimination (Area under the curve (AUC)) and by comparing observed and predicted numbers of fractures (comparing number of observed versus predicted fractures). This is the first study addressing the added value of BMD to FRAX® predictive performance.

Results

During a mean (SD) follow up of 9.12 (1.5) years, 178 first major osteoporotic (MOP) fractures and 28 first hip fractures were observed. The predictive performance of FRAX® in the sample was superior to that of BMD alone for both MOP and hip fractures. The AUC of FRAX® without BMD for was 0.76, 95%CI 0.72–0.79 for MOP fracture and 0.78, 95%CI 0.69–0.86 for hip fracture. No significant improvements were found when BMD was added to FRAX® clinical variables (p=0.25) for prediction of MOP (0.78, 95%CI 0.74–0.82) and hip (p=0.72)(0.79, 95%CI 0.69–0.89) fractures.

The AUC's for FRAX® (with and without BMD) were greater for men than for women. FRAX®, with and without BMD tended to underestimate the number of MOP fractures and to overestimate the number of hip fractures in females. In men, the number of observed fractures, both MOP and hip fractures, was within the 95CI of the predicted number by FRAX®, both with and without BMD. Agreement regarding observed and predicted MOP fractures was higher in those aged > 75 years compared to younger age groups, but it was generally good in all age groups for hip fractures.

Conclusion

FRAX® without BMD provided good fracture prediction, especially for males and for hip fractures. Adding BMD to FRAX® did not improve the predictive performance of the tool in the general population.

INTRODUCTION

Osteoporotic fractures currently represent an enormous social and economic burden worldwide,[1] which will tend to increase persistently due to the progressive ageing of the population and other societal changes,[2] unless effective preventive measures are taken.

Preventive strategies should be based on the absolute risk of osteoporotic fractures in the individual patient in order to seek the highest possible cost-effectiveness. FRAX®, [3 4] developed by the World Health Organization (WHO), is the most widely used tool to estimate osteoporotic fracture probabilities[5] and it has been incorporated in a large number of guidelines for the prevention and management of osteoporosis.[2 6-9] FRAX® estimates are based on a set of easily assessable clinical risk factors, with or without consideration of femoral neck bone mineral density (BMD),[4] making it a feasible tool, even in technically deprived environments.

Given the differences in the incidence of major osteoporotic (MOP) fractures between countries,[10 11] FRAX® should be validated in national cohorts to optimize its predictive value in each country.[4] A recent systematic review [12] demonstrated that this has not always been done and that most validation studies have significant bias, especially recruitment bias regarding the target population, and missing data on clinical risk factors. Few of these studies, worldwide, have been conducted in the general population.[12]

The purpose of this study was to evaluate the performance of the Portuguese version of FRAX® in predicting the 10-year probability of osteoporotic fractures using data from three prospective cohorts from the general population in Portugal. We also investigated the value of adding BMD to the clinical parameters of FRAX®.

METHODS

For this study, data of three different Portuguese cohorts, SAOL, IPR and EPIPorto (from Center, South and North of the country, respectively) were combined. Only persons aged > 40 years and with a complete set of data on FRAX® clinical risk factors were included. There were no other exclusion criteria. Figure 1 shows the disposition of participants during follow up and data analysis.

SAOL cohort

The SAOL (Santo António dos Olivais) study is a population-based cohort, designed to examine the association between a variety of potential risk factors and osteoporosis and fragility fractures. Design and recruitment have been previously described.[13-15] From March 1998 to April 2000, 1,745 persons, aged >18 years, were identified, contacted and recruited,

with the method of random numbers selection from the electoral register of the county, stratified by gender and 5-year age strata. Participants responded to validated questionnaires on risk factors for osteoporosis and underwent a DXA examination of the lumbar spine and proximal femur. Between March 2011 and March 2014, a follow up visit was done by a research nurse, who applied the questionnaires also used at baseline and performed DXA examination.

IPR cohort

The population of this prospective cohort study consists of 819 women and men aged 40 years or older at baseline, of whom a DXA was performed between December 1999 and July 2001 at IPR (Instituto Português de Reumatologia, Lisbon). Participants responded to a dedicated questionnaire on risk factors for osteoporosis and fracture. There were no predefined criteria for ordering a DXA, the request being based solely on judgment of the responsible clinician. Participants were referred by general practitioners, rheumatologists, endocrinologists, orthopedic surgeons, and gynaecologists, among others. Participants were invited for a follow up visit which took place between September and December 2014 by a research nurse who applied a questionnaire about fractures and osteoporosis treatment, specially designed for the purposes of this study.

EPIPorto cohort

The EPIPorto study is a population-based cohort study, with the aim of assessing determinants of health in the adult population of Porto. For this purpose, 2485 community-dwellers aged >18 years, selected in 1999-2003 by random digit phone dialing, have been repeatedly evaluated. Design and recruitment have been previously described.[16] The first evaluation did not include assessment of data on glucocorticoid intake and secondary osteoporosis. The second evaluation, performed in 2005-2006, including 1466 persons, recorded all clinical parameters relevant to FRAX®. We decided to use clinical parameters collected in the second evaluation, thus preferring to have a shorter follow up (mean average 7.43 years) than an incomplete set of predictors. No imputation was used for the missing follow-up time. Baseline DXA evaluation of 198 participants was available.
A third follow up visit took place between June 2013 and December of 2014, performed by a well-trained research team and included a questionnaire, especially designed for the purposes of this study, on fractures and treatments for osteoporosis.

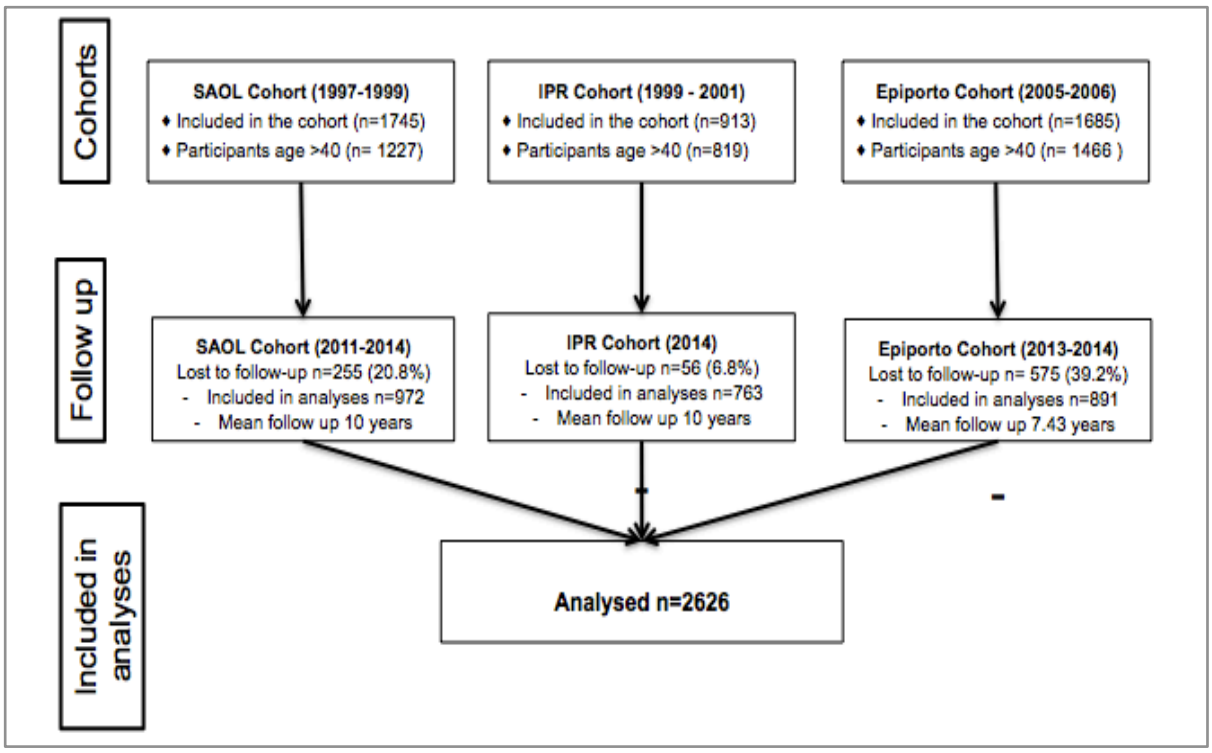

Figure 1. Disposition of participants in the three prospective cohort studies.

Bone mineral density evaluation

Dual energy X-ray absorptiometry (DXA) scans of the spine and proximal femur of the non-dominant side were performed at the baseline visit of all participants, using a Hologic QDR 4500/c bone densitometer in all cases. Participants without femoral BMD measurement at baseline were excluded. Hip T-scores were used as provided by the bone densitometer on the basis of NHANES III reference values[17].

Fractures

New first fractures and the date on which they occurred were self-reported at the follow-up visit in all cohorts. In the SAOL cohort, fracture reports were confirmed by clinical file review. in all but 2 of 52 fractures.

The fracture outcome of interest in this analysis was new first hip fracture and fracture of either the hip, wrist, shoulder, or clinical fracture of the spine (MOP), regardless of the degree of trauma, so as to conform to the definition of hip, and major osteoporotic fracture by FRAX.

FRAX® predictions

The 10-year fracture risk estimates for hip and MOP fractures (with and without adding the variable femoral neck BMD) for each individual case were assessed using the Portuguese

version of the FRAX® tool, by an operator that was blinded for the fracture outcomes.
All 3 cohort studies had been approved by local Ethics Committees and informed consent had been obtained from all patients. The Research Ethics Board of Faculty of Medicine of Coimbra University approved the current analysis.

Statistics

Follow-up time for the fracture analyses was truncated at 10 years, when applicable, to correspond with the 10-year fracture risk estimates from FRAX. In the case of participants deceased during follow up, fracture data was collected from family members and included in the analyses, according to the assumption of the tool[10]. Data for survival analyses was censored at the date of first fracture, date of death or ten years without fractures or end of follow-up before 10 years without fractures (as described in methods, participants from EPIPorto did not complete 10 years of follow-up).
Descriptive statistics for demographic and baseline characteristics are presented as mean (SD) or median (interquartile range) for continuous variables or count (percentage) for categorical variables.
Crude comparisons of parameters of participants with fractures versus those with no fractures were performed with Chi-square tests and independent – samples T tests.
Cox proportional hazards models were constructed for MOP and for hip fracture. prediction to assess the contributions of the individual FRAX® variables; in the SAOL cohort, we also assess the contribution of variables “falls during the past year” and “diabetes type I or type II”. Cox proportional hazards takes time into account, thus the shorter duration of follow up in EPIPorto was not an issue for those who had a first new fracture during this follow-up.
Receiver-operating characteristic (ROC) area under the curve (AUC) analyses were conducted to explore the fracture risk stratification using FRAX® with and without BMD and the prediction of BMD alone (femoral neck T-score or minimum value at any site). An AUC of 0.50 indicates a result no better than chance, an AUC<0.6 poor discriminative value, 0.6 to 0.8 moderate discriminative value, and >0.8 high discriminative value.[18] Negative discriminative function would be valued according to the mirror numbers (ie AUC >0.4; 0.2 to 0.4 and <0.2, respectively). In any case, only AUC’s with CI excluding 0.5 have discriminative value. Pairwise comparison of AUC’s ROC was performed using MedCalc (Version 14.8.1). Sensitivity analyses were performed by excluding data from EPIPorto given their shorter follow-up. Kaplan Meier curves were plotted, showing fracture incidence over time by cohort.
We assessed the fit of predicted values of FRAX® by comparing the observed proportion of participants who sustained a fracture with the proportion predicted by FRAX®. These analyses were undertaken in the entire cohort and then repeated in the cohort divided into

clinically relevant subgroups for age and gender.

Statistical analyses were performed with SPSS for Windows (Version 20.0, SPSS, Inc., Chicago, IL, USA). We applied STROBE criteria for cohort studies to ensure the quality of our study.[19] A p-value of <0.05 was taken as statistically significant.

RESULTS

The study sample with baseline and follow-up observations consisted of 2626 participants [1943 women (73%) and 683 (27%) men]. Baseline characteristics are summarized in Table 1. The mean (SD) age at baseline was 58.2 (10.2) years; during follow-up, 292 (11.1%) participants had died from different causes. The most prevalent among FRAX® clinical risk factors was "secondary osteoporosis" (24.3%) and the least prevalent was rheumatoid arthritis (4.9%).

During follow-up, with a mean (SD) duration of 9.12 (1.5) years (minimum and a total 23949 person/years, 28 (1.1%) of these participants suffered from an incident hip fracture [median FRAX®-estimated risk at baseline for hip fracture: without BMD 2.8%(1.4-4.8); with BMD 6.9%(1.9-11.8)] and 178 (6.8%) had an incident MOP [median FRAX®-estimated risk at baseline for MOP: without BMD 6.7%(3.9-10); with BMD 8.9%(5.2-14)]. More details can be found in Supplementary Table 1.

Table 1. Baseline characteristics of participants and baseline FRAX® risk estimates.

	All	Men	Women
N, n (%)	2626	683 (27)	1943 (73.0)
Age, mean (SD)	58.2 (10.2)	60.3 (11.4)	57.7 (9.9)
40-59, n (%)	1495 (56.9)	352 (51.5)	1143 (58.8)
60-74, n (%)	950 (36.2)	260 (38.1)	690 (35.5)
≥75, n (%)	181 (6.9)	71 (10.4)	110 (5.7)
BMI, mean (SD)	27.3 (4.5)	75.5 (11.9)	66.4 (11.6)
Previous Fracture, n (%)	512 (19.5)	153 (22.4)	359 (18.5)
Parent Hip fractures, n (%)	213 (8.1)	50 (7.3)	163 (8.4)
Current smoking, n (%)	612 (23.3)	344 (50.4)	268 (13.8)
Oral glucocorticoids, n (%)	182 (6.9)	38 (5.6)	144 (7.4)
Rheumatoid arthritis, n (%)	128 (4.9)	18 (2.6)	110 (5.7)
Secondary osteoporosis, n (%)	639 (24.3)	46 (6.7)	593 (30.5)
Alcohol 3 or more units day, n (%)	529 (20.1)	287 (42)	242 (12.5)
Femoral Neck T Score, mean (SD) #	-1.54 (1.31)	-1.35 (1.40)	-1.58 (1.30)
≥ - 1, n (%)	595 (31.4)	138 (37.7)	457 (29.9)
- 2,5 < T < -1, n (%)	867 (45.7)	152 (41.5)	715 (46.7)
≤ -2,5, n (%)	435 (22.9)	76 (20.8)	359 (23.4)
Median 10 year probability, median (IQR)			
MOP fracture without BMD	2.9 (1.7-5.8)	1.6(1.6-4.4)	3.0(1.7-6.2)
MOP fracture with BMD	3.4 (1.8-6.9)	3.1(1.7-6)	3.5 (1.9-7)
HIP fracture without BMD	0.5 (0.2-1.6)	0.5 (0.2-1.6)	0.5 (0.2-1.6)
HIP fracture with BMD	0.7 (0.2-2.5)	0.95(0.28-2.93)	0.6 (0.2-2.3)

There were no missing data for any of the clinical risk factors considered by FRAX®.
IQR, Inter quartile range; SD, standard deviation.
Femoral Neck BMD was available for 1897 participants.

In Table 2, we present the ROC AUC for FRAX® estimates, with and without BMD, as well as for DXA alone. The performance of FRAX® is superior to DXA alone for both MOP and hip fractures, in both men and women. Please see supplementary figure 2 and 3.
AUCs achieved by FRAX® were numerically higher with than without DXA, with the exception of hip fractures in men, but none of these differences reached statistical significance. AUCs achieved by FRAX® with DXA, were superior to those of DXA alone, all differences being statistically significant. ROC analyses excluding participants from EPIPorto revealed exactly the same AUC values, except for a modest increase for hip prediction with BMD (AUC 0.80, 95% CI 0.71-0.89 (data not show).

Table 2. ROC area under the curve (AUC) analyses for hip and major osteoporotic fractures.

	Hip fractures			Major Osteoporotic fractures		
	AUC	95% CI	p value	AUC	95% CI	p value
WOMEN						
BMD Femoral neck alone	0.68	0.66-0.71	<.009	0.66	0.63-0.68	<.001
FRAX® without BMD	0.72 a ns	0.69-0.74	<.001	0.75 a***	0.73-0.77	<.001
FRAX® with BMD	0.75 a** b ns	0.62-0.87	<.001	0.76 a*** b ns	0.74-0.78	<.001
MEN						
BMD Femoral neck alone	0.82	0.78-0.86	<.004	0.80	0.76-0.84	<.001
FRAX® without BMD	0.93 a***	0.89-0.95	<.001	0.81 a ns	0.76-0.85	<.001
FRAX® with BMD	0.90 a*** b ns	0.86-0.93	<.001	0.85 a* b ns	0.81-0.88	<.001
BOTH						
BMD Femoral neck alone	0.72	0.61-0.83	<.001	0.69	0.64-0.73	<.001
FRAX® without BMD	0.78	0.69-0.86	<.001	0.76 a***	0.72-0.79	<.001
FRAX® with BMD	0.79 a*** b ns	0.69-0.89	<.001	0.78 a*** b ns	0.74-0.82	<.001

a - p value vs same site/gender BMD alone; b - p value vs same site/gender FRAX® without BMD: ns- non-significant; * p<.05; ** p<.01 ; *** p<.001

As shown in Table 3 when BMD was not included in the model, all clinical risk factors except BMI and rheumatoid arthritis were independent predictors of major osteoporotic fractures. Regarding hip fractures, the model without BMD still retains age and glucocorticoids as significant predictors associated with a history of parent hip fractures.

When BMD was included in the model (Table 4), age, glucocorticoids, parent hip fractures, previous osteoporotic fracture, current smoking, secondary osteoporosis and femoral neck BMD were all independent predictors of major osteoporotic fractures in our sample. Parental hip fractures showed the largest predicted risk for MOP fracture (HR 3.69, 95%CI 2.51-5.43) and BMD the smallest (HR 0.72, 95%CI 0.62-0.83) in the model with BMD.

The only independent predictors of hip fractures were age, BMI and femoral neck BMD. Gender, alcohol usage, secondary osteoporosis and rheumatoid arthritis were not independently associated with either MOP or hip fractures.

Table 3. Hazard Ratios (HRs) for fracture based on individual FRAX® variables excluding BMD. All variables are defined as prescribed by FRAX®.

	Hip fractures			**Major osteoporotic fractures**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Sex (men vs women)	0.80	0.31-2.08	0.642	1.64	1.05-2.55	0.030
Age (years)	1.13	1.08-1.18	<.001	1.04	1.02-1.06	<.001
BMI (Kg/m^2)	1.05	0.97-1.14	0.204	0.98	0.94-1.01	0.206
Previous Fracture(Y/N)	1.44	0.62-3.33	0.393	2.75	2.02-3.75	<.001
Parent Hip fractures (Y/N)	3.29	1.31-8.19	0.011	3.51	2.48-4.98	<.001
Current smoking (Y/N)	0.95	0.29-3.12	0.931	1.32	0.87-2.01	0.196
Glucocorticoids (Y/N)	3.33	1.23-9.06	0.018	2.99	1.95-4.59	<.001
Rheumatoid arthritis (Y/N)	1.44	0.38-5.48	0.594	1.67	0.98-2.84	0.058
Secondary osteoporosis (Y/N)	1.34	0.56-3.22	0.514	1.61	1.17-2.23	0.004
Alcohol 3 or more units day (Y/N)	0.82	0.27-2.48	0.722	1.52	1.04-2.21	<.030

Table 4. Hazard Ratios (HRs) for fracture based on individual FRAX® variables including femoral neck BMD

	Hip fractures			**Major osteoporotic fractures**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Sex (men vs women)	0.58	0.21-1.59	0.287	1.32	0.80-2.20	0.276
Age (years)	1.12	1.07-1.18	<.001	1.03	1.01-1.05	0.006
BMI (Kg/m^2)	1.14	1.04-1.25	0.007	1.01	0.97-1.05	0.598
Previous Fracture(Y/N)	1.23	0.48-3.11	0.669	2.47	1.72-3.55	<.001
Parent Hip fractures (Y/N)	1.44	0.42-4.95	0.560	3.69	2.51-5.43	<.001
Current smoking (Y/N)	2.45	0.69-8.68	0.165	1.72	1.05-2.81	0.031
Glucocorticoids (Y/N)	2.62	0.92-7.49	0.072	2.80	1.78-4.41	<.001
Rheumatoid arthritis (Y/N)	1.68	0.42-6.69	0.461	1.36	0.74-2.48	0.318
Secondary osteoporosis (Y/N)	1.22	0.48-3.09	0.673	1.43	1.00-2.05	0.049
Alcohol 3 or more units day (Y/N)	1.14	0.32-4.11	0.842	1.30	0.78-2.17	0.323
Femoral Neck T Score	0.60	0.41-0.87	0.007	0.72	0.62-0.83	<.001

The impact of the variables “falls in the last year” and “Diabetes type I or type II” upon the risk of fractures was assessed in the SAOL cohort (the only one providing this data) in multivariate hazard ratios analyses adjusted for all variables included in FRAX. These potential risk factors were reported in 248 and 152 on the 972 participants. Neither “falls in the last year” nor “Diabetes type I or type II” were significant independent risk factors in this cohort. See supplementary table 2 and 3.

Table 5 shows the calibration of each calculator by comparing the number of observed first new fractures and the at baseline estimated risk by FRAX® (IC95). FRAX® with and without BMD underestimated incident MOP and overestimated hip fractures in women. In men the observed rates of first new fractures were within the 95CI of baseline FRAX® predicted rates.

Regarding age and considering both genders together, the observed number of hip fractures was within the 95CI of prediction in all ages groups, with the exception of underestimation of the FRAX® with BMD estimate for the group aged <60 years. For MOP fractures, the baseline FRAX® estimate also underestimated the risk for those under the age of 75. The agreement between predicted and observed rats above this age was better, although the

number of observed new first fractures was small.

Kaplan Meier survival models showed that a similar number of new first fractures occur every year in all 3 cohorts (data not shown). Based on this observation we estimated that 12 MOP fractures would have occurred in the 2.5 missing years of follow-up in EPIPorto, which are unaccounted for. The impact of this difference of follow-up was evaluated through sensitivity analysis, as described above.

Table 5. FRAX®-estimated and observed number of first new fractures during follow-up

	FRAX® without BMD (n=2626)		**FRAX® with BMD (n=1986)**	
	Observed	**Estimated (CI 95%)**	**Observed**	**Estimated (CI 95%)**
Women				
MOP	145	97.5 (78.6-116.3)	116	91.3 (73.1-109.4)
Hip	20	30.9 (20.1-41.8)	17	35.8 (24.2-44.4)
Men				
MOP	33	24.9 (15.3-34.6)	23	18.9 (10.6-27.2)
Hip	8	9.9 (3.82-16.1)	7	10.3 (4.1-16.5)
Women and Men				
MOP	178	122.4 (101.3-143.6)	139	116.2 (95.7-136.7)
Hip	28	40.9 (28.4-53.3)	24	48.7 (35.2-62.2)
Age <60 years				
MOP	69	34.7 (23.3-46.1)	52	36.8 (25.1-48.5)
Hip	1	5.5 (0.9-10.1)	1	12.4 (5.5-19.2)
Age 60-75 years				
MOP	97	67 (51.5-82.5)	77	60.4 (45.9-75)
Hip	21	24.1 (14.6-33.7)	18	26.3 (16.5-36.1)
Age >75 years				
MOP	12	21 (12.7-29.3)	10	13.7 (7.08-20.3)
Hip	6	11.4 (5.06-17.8)	5	7.8 (2.6-13)

DISCUSSION

In this study, we used several approaches to compare the predictive performance of baseline FRAX® estimates with and without BMD with observed first new fractures during follow-up in a cohort of general population.

AUC ROC values of baseline FRAX® estimates ranged from 0.78 to 0.79 for hip fracture and 0.76 to 0.78 for major osteoporotic fracture, indicating moderate discriminative ability of FRAX®, without and with BMD, for predicting both hip and osteoporotic fractures in both genders. The AUC ROC values for BMD alone were 0.72 for hip fractures and 0.69 for MOP fracture. FRAX® estimates with and without BMD have a better performance than has BMD alone. No significant differences were found between the predictive performance of FRAX® estimates with and without BMD.

The prediction of first new hip fractures was more reliable than that of MOP fractures, which is in agreement with previous studies.[20-26] The performance of the tool was higher in males than in females, for both groups of fractures.[22 27]

AUC ROC values found in our study are generally higher than those found in a recent meta-analysis.[12] This may be related to the higher quality of methods used in our study and the full respect for the conditions of FRAX® applicability predicted in its development process:[4 10] in contrast with most previous studies, we included participants from the general population, considered all clinical risk factors included in FRAX® using the exact definitions provided by the tool, only included cases with a complete set of clinical data, and accounted for participants who died during follow up. Our only limitation is this respect was the slightly shorter duration of follow-up in one of the cohorts. The prevalence of clinical risk factors was similar to other studies, with exception of secondary osteoporosis and consumption of alcohol and tobacco which were higher in our study. We also found that the individual risk factors used by FRAX® had significant independent contributions to fracture prediction. Age and glucocorticoid use were strongly associated with new first MOP and hip fracture risk in both models (with and without BMD). Adding the variables “falls in the last year” and “Diabetes type I or type II” to the models with FRAX® with and without BMD in one of the three cohorts did not result in improved prediction, but the numbers included in this analysis are too small to allow definite conclusions.

FRAX®, with and without BMD, underestimated incident MOP and overestimated hip fractures in women, while in men the observed number of both types of fractures was within the 95% confidence interval of the prediction, both with and without BMD. These results are similar with those found in other studies[20 24 25 28 29] and a systematic review.[30] We hypothesize that the discrepancies between the observed and predicted rates of fractures in females may be related to the fact that for the construction of Portuguese FRAX® algorithm we have only used actual national epidemiologic data for hip fractures, the rate for the MOP fractures being estimated using Swedish age specific ratios.[31] When considering age, the number of observed first new MOP fractures was higher than estimated until the age of 75. There was good agreement regarding hip fractures in all age groups.

Overall, our results show that the FRAX® algorithm with clinical risk factors has a better performance at predicting the rate of first new fractures than BMD alone. This is in agreement with previous studies.[3 22] They also demonstrate that adding BMD to the clinical risk factors brings no improvement to FRAX® prediction, in terms of AUC ROC or rates of observed vs predicted fractures. This is the case in both men and women, MOP and hip fractures. The impact of DXA upon FRAX® performance has, to the best of our knowledge,

not been investigated before. Our observations question the cost-effectiveness of DXA measurements for the purpose of predicting fractures in the general population.

Some limitations of this study need to be acknowledged. Our dropout rate was 25.2%, which is considerable, although similar to that reported in other prospective cohort studies. Fracture events were self-reported and only confirmed in the SAOL cohort by clinical file review. During follow-up, 7.6% of participants used bisphosphonates at some time. Such treatment may have prevented some fractures, potentially contributing to the overestimation of the fracture risk. We investigated the performance of FRAX® Portugal, we are unable to comment on the calibration or discrimination of other country-specific FRAX® tools. Follow-up in the EPIPorto cohort was shorter than the 10-year timeline of FRAX®. This did not have a relevant impact regarding the ROC analyses but may have artificially reduced, although slightly, the underestimation of the actual number of fractures by FRAX®.

Our study has several strengths: it is a multicentric cohort of participants recruited from the general population, the average duration of follow-up was 8.7 years, the clinical risk factors included in FRAX® were collected in all participants and, we also considered death hazard. These qualities support the validity of the results in the population expected to receive the test in daily practice.

CONCLUSION

A moderate performance of FRAX® was found in both men and women, with higher AUCs ROC than those reported in the derivation and validation cohorts studied by the WHO Collaborating Centre[3] and considered in a recent meta-analyses.[12] The performance was better for hip than for MOP fractures, in males than in females, and in participants over the age of 75. Adding BMD to the model did not improve FRAX® performance. The Portuguese FRAX® tool is considered suitable for clinical use in Portugal.

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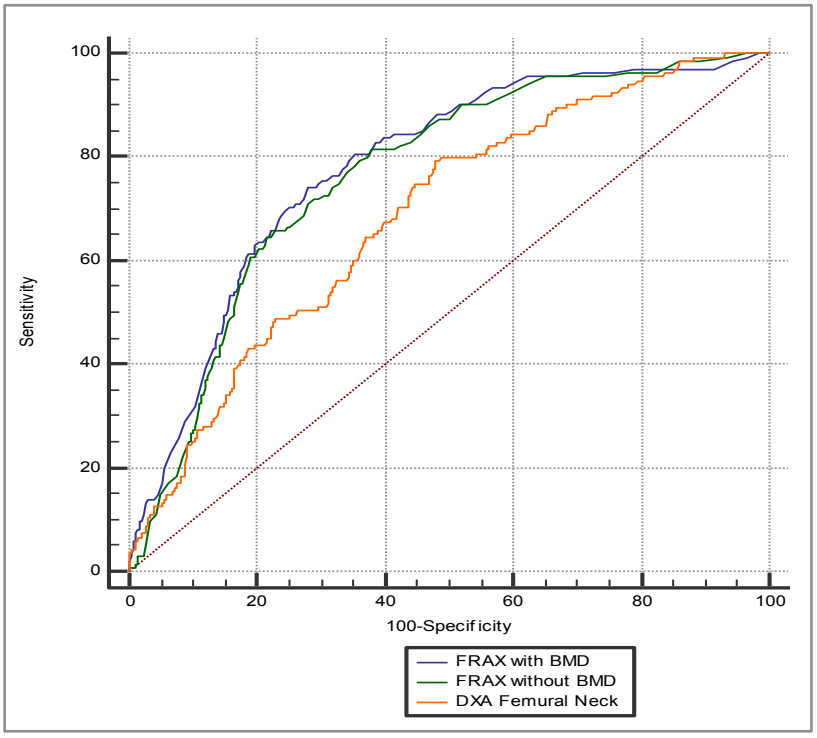
SUPPLEMENTARY MATERIAL

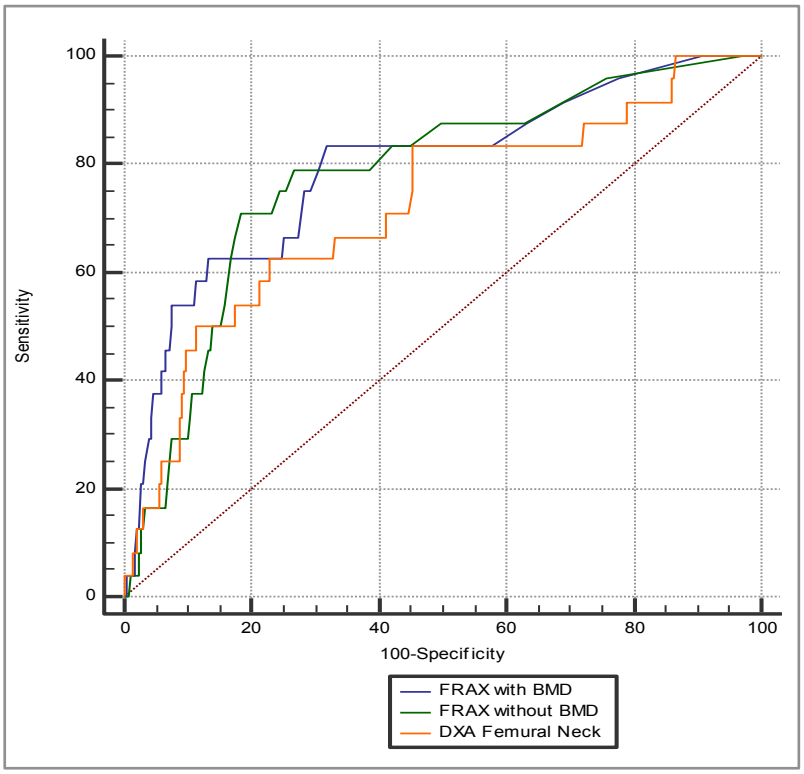
Supplementary Table 1. Baseline characteristics of participants with and without fracture including FRAX® risk estimates, there were no missing data for any of the clinical risk factors.

	With fracture (n=178)	**Without fracture (n=2,448)**	**p value**
Gender (Female), n (%)	145 (81.5)	1,798 (73.4)	<.01
Age, mean (SD)	62 (8.7)	58 (10)	<.001
40-60, n (%)	68 (38.2)	1427 (58.3)	<.001
60-75, n (%)	95 (53.4)	855 (34.9)	<.001
>75, n (%)	15 (8.4)	166 (6.8)	<.001
BMI, n (%)	26.9 (4.5)	27.3 (4.4)	0.22
Previous Fracture, n (%)	72 (40.4)	440 (18.0)	<.001
Parent Hip fractures, n (%)	21 (11.8)	170 (6.9)	<.001
Current smoking, n (%)	37 (20.8)	575 (23.5)	0.46
Glucocorticoids, n (%)	35 (19.7)	147 (6.0)	<.001
Rheumatoid arthritis, n (%)	21 (11.8)	107 (4.4)	<.001
Secondary osteoporosis, n (%)	66 (37.1)	573 (23.4)	<.001
Alcohol 3 or more units day, n (%)	41 (23)	488 (19.9)	0.33
Femoral Neck T Score, mean (SD) #	-2.31(1.1)	-1.48 (1.3)	<.001
≥ - 1, n (%)	15 (10.8)	580 (33)	<.001
- 2,5 < T < -1, n (%)	64 (46)	803 (45.7)	<.001
≤ -2,5, n (%)	60 (43.2)	375 (21.3)	<.001
Median 10-year probability, median (IQR)			
MOP without BMD	6.7 (3.9-10)	2.7 (1.6-5.3)	<.001
MOP with BMD	8.9 (5.2-14.0)	3.2 (1.8-6.2)	<.001
HIP without BMD	1.6 (0.7-3.9)	0.5 (0.2-1.5)	<.001
HIP with BMD	2.8 (1.0 -6.8)	0.6 (0.2-2.1)	<.001

Femoral Neck BMD was available for 1897 participants.



Supplementary Figure 2. Comparison of ROC curves for 10-year probability of a major osteoporotic fracture (both genders) estimated by FRAX® with and without BMD and for DXA alone.



Supplementary Figure 3. Comparison of ROC curves for 10-year probability of hip fracture (both genders) estimate by FRAX® with and without BMD and for DXA alone.

Supplementary Table 2 – Hazard Ratios (HRs) for MOP Fracture Based on Individual FRAX® Variables, falls in the last year and Diabetes type I or type II excluding BMD

	Osteoporotic fractures		
	HR	**95% CI**	**p Value**
Sex (men vs women)	1.83	0.76-4.40	0.175
Age	1.05	1.02-1.08	0.003
BMI	1.05	0.99-1.11	0.114
Previous Fracture	1.68	0.86-3.28	0.131
Parent Hip fractures	2.09	1.10-3.97	0.024
Current smoking	2.42	1.12-5.23	0.025
Glucocorticoids	2.11	0.89-5.03	0.092
Rheumatoid arthritis	1.65	0.22-12.23	0.626
Secondary osteoporosis	2.38	1.34-4.23	0.003
Alcohol 3 or more units day	2.09	1.00-4.38	0.051
Falls	1.28	0.72-2.30	0.404
Diabetes	1.06	0.73-1.56	0.759

Supplementary Table 3 – Hazard Ratios (HRs) for MOP Fracture Based on Individual FRAX® Variables, falls in the last year and Diabetes type I or type II including Femoral Neck BMD

	Osteoporotic fractures		
	HR	**95% CI**	**p Value**
Sex (men vs women)	1.54	0.64-3.70	0.330
Age	1.02	0.99-1.06	0.263
BMI	1.09	1.02-1.16	0.008
Previous Fracture	1.68	0.86-3.29	0.132
Parent Hip fractures	1.90	1.00-3.62	0.050
Current smoking	2.26	1.04-4.90	0.040
Glucocorticoids	2.57	1.06-6.18	0.036
Rheumatoid arthritis	1.74	0.23-13.04	0589
Secondary osteoporosis	2.27	1.28-4.03	0.005
Alcohol 3 or more units day	2.19	1.05-4.60	0.037
Femoral Neck T Score	0.63	0.46-0.86	0.004
Falls	1.28	0.71-2.31	0.414
Diabetes	1.11	0.76-1.63	0.595

Chapter 5

THE BURDEN OF OSTEOPOROTIC HIP FRACTURES IN PORTUGAL: COSTS, HEALTH RELATED QUALITY OF LIFE AND MORTALITY

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Marques A, Lourenço O, da Silva JAP and on behalf of the Portuguese Working Group for the Study of the Burden of Hip Fractures in Portugal. The burden of osteoporotic hip fractures in Portugal: costs, health related quality of life and mortality. Osteoporos Int 2015; 26(11): 2623-30.

ABSTRACT

Introduction

Osteoporotic fractures represent a remarkable burden to health care systems and societies worldwide, which will tend to increase as life expectancy expands and life style changes favour osteoporosis. The cost-effectiveness evaluation of intervention strategies demands accurate data on the epidemiological and economical reality to be addressed.

Methods

Information was collected retrospectively on consumption of resources and changes in quality of life attributable to fracture as well as mortality, regarding 186 patients randomly selected to represent the distribution of hip fractures in the Portuguese population, in terms of gender, age and geographical provenience. Data were cross-tabulated with socio-demographic variables and individual resources consumption to estimate the burden of disease. A societal perspective was adopted, including direct and indirect costs. Multivariate analyses were carried out to assess the main determinants of Heath-related Quality of Life (HrQoL).

Results

Mean individual fracture-related costs were estimated at €13,434 [12,290; 14,576] for the first year and €5,985 [4,982; 7,045] for the second year following the fracture. In 2011 the economic burden attributable to osteoporotic hip fractures in Portugal could be estimated at €216 million. Mean reduction in Health-related quality of life 12 months after fracture was estimated at 0.34. Regression analysis showed that age was associated with a higher loss of HrQoL, whereas education had the opposing effect. We observed 12% excess mortality in the first year after hip fracture, when compared to the gender and age-matched general population.

Conclusions

Results of this study indicate that osteoporotic hip fractures are, also in Portugal, despite its low incidence of fractures and cost per event, associated with a high societal burden, in terms of costs, loss in Health-related quality of life and mortality. These data provide valuable input to the design and selection of fracture prevention strategies.

INTRODUCTION

Osteoporotic fractures impact an enormous burden upon societies, due to costs related to immediate treatment and also to the management of their long-term consequences in terms of disability, comorbidity and mortality.

It has been estimated that the annual number of osteoporotic fractures in the European Union will rise from 3.5 million in 2010 to 4.5 million in 2025, corresponding to an increase of 28%.[1] The annual worldwide direct and indirect costs of hip fractures have been calculated at $34.8 billion in 1990, and are expected to rise to an estimated $131 billion by 2050.[2]

This burden and its prospected increase impose the need for careful evaluation of the cost-effectiveness of different intervention strategies. These strategies need to be adapted to the actual epidemiological and economical reality they intend to address, as it can be quite diverse.[3] Portugal has a relatively low incidence of osteoporotic hip fractures at around 206 cases per 100.000 population aged 40+.[4] The management of osteoporotic fractures, as well as the cost of treatment, can also vary.[5]

Hip fractures are a useful surrogate for determining the overall burden of osteoporosis, as they are more readily identified in hospital discharge registers. Studies performed in countries with reliable registers of all types of fractures are typically used to extrapolate from data obtained with hip fractures.[1] However, detailed cost-of-illness (COI) studies regarding hip fractures must be performed in each country if locally valid guidance and conclusions are to be drawn.

To the extent of our knowledge, this is the first study to estimate the overall societal cost of hip fractures, the per-patient costs and the impact on Heath-related quality of life in Portugal, based on real-life individual patient data.

METHODS

In this study we adopt a prevalence-based approach time.[6] We took a societal perspective in the measurement of costs.[6] Data on resource consumption over the two years following the fracture was collected retrospectively regarding fractures occurred 24 to 30 months before the interview. Patients themselves or their primary caregivers provided the information. By “primary caregiver” we mean the person responsible for managing the care of the patient, i.e. the family member or trained professional who took care of medication, personal support and medical appointments throughout the two years of interest. If such a person could not be clearly identified, the patient was excluded and another one recruited.

A draft version of the questionnaire was tested in ten individuals and adaptive corrections were introduced into the final version, as recommended.[7 8] The first part of the questionnaire covered patient's socio-demographic data and the quantities of resources consumed over the two-year period following fracture or until death. The second part of the questionnaire aimed to assess the patients' HrQoL. We used the EQ-5D instrument in the version validated for the Portuguese population, that contain a Portuguese tariff.[9] These questions were focused onto three different moments: 1) before the hip fracture, 2) one month after the fracture and 3) one year after the fracture. The interviews were conducted by telephone by three trained interviewers (AM; IL; JS) and took, on average, 25 minutes. Participants were asked to identify solely expenses incurred as a consequence of fracture and none other.

The resources consumed by patients were categorised into direct medical costs (inpatient care; rehabilitation care; outpatient consultations; osteoporosis preventive medications; diagnostic tests; nursing care), and direct non-medical costs (long-term care; nursing home; patient's transportation; technical aids; home adaptations, home care, informal care, burial) as performed by several authors.[3 7 10 11] Costs associated with productivity changes due to the hip fracture were also included in the analysis.[12] Information regarding the definition of resources and their unit cost is provided in supplementary material (Table 1).

Participation was explicitly voluntary and ethical approval was obtained from the Ethical Committee of the Faculty of Medicine of Coimbra University.

Power calculations

In the calculations for the sample size, performed to establish the minimum number of patients required to ensure reliability of the national estimates of the mean cost per fracture, we decided to assume a range of total costs between €2,500[i] and €20,000[ii] for the first year, thus deriving an estimate of the SD of about 4,375[iii]. Establishing an absolute maximum error of estimation on €800,[iv] not to be exceeded with higher than 5% probability, the sample size required is 114 units.[v] Due to the uncertainty in the population's SD estimate, we planned to include 186 patients (Details on the statistical calculations employed can be found on references.[13 14]

[i] €2,500 correspond to the comprehensive cost of inpatient care to treat a hip fracture. Table 1 shows the source of this figure.

[ii] €20,000 corresponds approximately to the upper 95% confidence interval for Sweden,[7] assuming the replacement costing method

[iii] Cochran[14] refer that and estimate of the SD can be found by computing the range divided by 4.

[iv] € 800 is approximately equivalent to 5% of the mean cost of hip fracture in Sweden,[7] assuming the replacement cost method

[v] The sample size estimation accounted for fact that we are extracting a random sample from a finite population.

Patient selection

We obtained demographic information about all osteoporotic hip fractures treated in Portuguese public hospitals in the year 2011, through the National Hospital Discharge Register. Public hospitals are estimated to take care of over 95% of all osteoporotic hip fractures in Portugal. Based on the observed cases, we designed a stratified random sampling method - the size of the sample in each stratum was proportionate to the size of the stratum in the population. We defined the following strata: geographical origin, gender and the age groups ≤74 years; 75 to 85 years; and ≥ 85. Twenty-six hospitals in Portugal mainland were selected and invited to collaborate in the study. Each hospital was requested to recruit a number of cases per strata proportionally equivalent to its representation in the national hip fracture case list 2011.

A representative from each hospital, typically the head of the Orthopaedics department, was asked to provide the contact of a pre-defined number of consenting patients of specific age × gender combination. These participants were randomly selected from within the full list of hip fracture victims locally treated in 2011, following a web-based random number generator. There were no exclusion criteria. Even patients who had died or were unable to answer were included if the primary caregiver remain the same over all the period of study. To decrease the likelihood of refusals and respect the principles underlying the ethical approval, the local hospital representative contacted directly the patient or caregiver, presented the goals of the project and asked for permission (consent) for a subsequent phone enquiry by the research team. In total, 212 individuals were selected according to these criteria. Twenty-six were excluded because of difficulties in contact (n=13), refusal (n=9) and unavailability or undefinition of primary caregiver (n=4). We confirmed that five of these twenty six patients had died since the fracture.

Statistical analysis

Information is summarized as arithmetic means with 95% confidence intervals (CI) or percentages as appropriate. When informative, we also display the standard deviation of some statistics. Student's t tests were conducted to compare means and two-proportion z test was adopted compare proportions.

The expected number of deaths in our sample was estimated on the basis of national gender and age-specific mortality rates. Our data contain the number of days until death after the hip fracture, we use this data to estimates the survival and to compare across groups we use the log-rank test [15]

A multiple linear regression model was used to analyse the relationship between HrQoL and a set of potentially relevant independent variables. Further information regarding the

definition of all variables and the methodology used in the regression models can be found in the supplementary material.

All statistical analyses were conducted using Stata, version 12.0.

RESULTS

We collected data from 186 patients. Demographic characteristics of participants are presented in Table 1. Mean age at fracture was 80.5 years and 78.5% of the respondents were female. These data, as well as the geographical distribution, correspond almost perfectly to the parameters of the total population that suffered hip fractures in Portugal over the year 2011 (Total N= 11,124, mean age 80.5 ± 9.9 years and 76% female, differences not statistically significant). On average, these patients had attended school for 3.5 years (SD 2.82). Prior to fracture, 85.5% resided on their own house, 10.2% lived with relatives and 4.3% already resided in a nursing home.

Table 1. Summary of patient demographics (n=186)

		n (%)
Gender	Female	146 (78,5)
	Male	40 (21.5)
Age	≤74	36 (19.4)
	≥75 <85	92 (49.4)
	≥85	58 (31.2)
Marital Status	Married	77 (41,4)
	Divorced	8 (4.3)
	Single	14 (7.5)
	Widowed	87 (46.8)
Residence prior to fracture	Own house	159 (85.5)
	With relatives	19 (10.2)
	Nursing home	8 (4.3)
Year of formal education	= 0	35 (18.8)
	≥0 ≤ 4	131 (70.4)
	>4	20 (10.8)

Resource use and costs

Table 2 presents the proportion of patients who used each type of resource as a consequence of the hip fracture. The likelihood of utilization of each type of resource is much higher during the first year following the facture than in the second year. Further to hospital

admission, nearly 100% visited a physician at least once and used diagnostic tests. Technical aids were purchased by 85% of patients, transportation by ambulance was used by 75.8% and 61.8% received rehabilitation care. Only 29.6% were treated with calcium and/or Vitamin D and 16.7% received other anti-osteoporotic agents within the 2 years following the fracture. After discharge from hospital, 18.3% of the patients were transferred to a long-term care facility and 19.9% to a nursing home; 18.3% of the patients needed home care support and 32.3% receive care from a nurse. During the second year, there was a marked decrease of the variety and quantity of resources used: no consumption of nursing care, technical aids, diagnostic tests and transportation, were reported as due to the hip fracture in the second year. Regarding family and friends' support, 62.9% of patients reported receiving an average of 32.9 hours by week of this type of care, as a consequence of the fracture, during the first year. Productivity losses were only reported by 4 patients - all the remaining participants were already retired.

Table 2. Patients making use of specific resources, due to hip fracture, by year of consumption. Percentage (n).

Resource	Year 1 (n=186)	Year 2 (n=148)
Rehabilitation care	61.8% (115)	8.06% (12)
Inpatient care	100% (186)	2.15% (3)
Medical consultations	97.3% (181)	45.9% (70)
Osteoporosis treatment	16.7% (31)	16.7% (25)
Calcium +Vitamin D	29.6% (55)	29.6% (44)
Diagnostic tests (x ray/Densitometry/ CTscan)	98.4% (183)	0%
Nursing care	32.3% (60)	0%
Long-term care	18.3% (34)	0.5% (1)
Nursing home	19.9% (37)	15.5% (23)
Home care	18.3% (34)	14.5% (21)
Technical aids	85% (158)	0%
Transportation	75.8% (141)	0%
Informal care	62.9% (117)	41.4% (61)
Productivity losses	2.15% (4)	0%

Table 3 presents an estimate of the cost (€), per patient and per year, for each type of resource considered, stratified by gender. Considering all resources, the average cost per patient, per year, for treating a hip fracture in Portugal is estimated at €13,434 for the first year and in €5,985 for the second year after the hip fracture. With reference to the first year, 28% of the total costs are due to direct medical costs, 70% due to direct non-medical costs and the remaining 2% are indirect costs due to productivity losses. During the second year there is a marked decrease of costs, the most relevant item being informal care (€3,549). Participants did not report any costs associated with transportation or technical aids in the

second year. The productivity loss cost category was only verified in four men and contributed and average of €194 for the total cost of each hip fracture.

Table 3. Costs in Euros, per patient and per year, for each type of resource considered.
The intervals in each cell represent the 95% confidence interval.

	Year 1	Year 2	Year 1 female	Year 1 male	Year 2 female	Year 2 male
			Direct medical costs			
Rehabilitation care	1,056 [845; 1,266]	179 [73; 285]	1,040 [799; 1,281]	1,115 [666; 1,563]	168 [61; 275]	221 [-94; 537]
Inpatient care	2,500	67 [8; 125]	2,500	2,500	51 [-6; 110]	125 [-51; 301]
Medical consultations	145 [127; 162]	47 [34; 59]	147 [127; 168]	136 [104; 169]	50 [35; 65]	30 [6; 53]
Osteoporosis treatment	54 [43; 66]	54 [43; 66]	61 [47; 74]	30 [12; 48]	61 [47; 74]	30 [12; 48]
Diagnostic tests (x ray Dens./CTscan)	31 [26; 35]	0	30 [26; 34]	34 [18; 50]	0	0
Nursing care	32 [24; 40]	0	31 [21; 40]	36 [20; 52]	0	0
Total direct medical costs	3,818 [3,603; 4,046]	347 [210; 484]	3,809 [3,569; 4,072]	3,851 [3,397; 4,304]	330 [192-450]	406 [-18; 849]
			Direct non-medical costs			
Long-term care	982 [606; 1,357]	172 [-167; 510]	1,008 [568; 14479]	887 [166; 1,607]	219 [-214; 652]	0
Nursing home	1,383 [939; 1,828]	1,114 [696; 1,533]	1,299 [804; 1,794]	1,691 [647; 2,734]	970 [535; 1,406]	1,640 [487; 2,792]
Home care	855 [477; 1,232]	803 [431; 1,175]	916 [467; 1,364]	632 [-31; 1,295]	850 [408; 1,291]	632 [-31; 1,295]
Technical aids	588 [395; 781]	0	599 [368; 830]	548 [220; 876]	0	0
Transportation	74 [48; 101]	0	71 [43; 100]	86 [20; 153]	0	0
Burial*	149 [90; 208]	0	163 [94; 233]	94 [-12; 201]	0	0
Informal care	5,391 [4,429; 6,352]	3,549 [2,718; 4,379]	5,628 [4,524; 6,732]	4,523 [2,519; 6,525]	3,870 [2,889; 4,851]	2,375 [919; 3,832]
Total direct non-medical costs	9,422 [8,339; 10,504]	5,638 [4,658; 6,618]	9,684 [8,452; 10,935]	8,461 [6,162; 10,696]	5,909 [4,785; 7,035]	4,647 [2,606; 6,688]
Productivity loss	194 [-16; 405]	0	0	904 [-77; 1885]	0	0
Total costs	13,434 [12,290; 14,576]	5,985 [4,982; 7,045]	13,493 [12,187; 14,814]	13,216 [10,782; 15,586]	6,239 [5,131; 7,476]	5,053 [5,131; 7,476]

* Only the costs of burials due to excess mortality were computed

We verified that variable type of respondent (caregiver/patient) does not have a significant influence upon costs or quality of life in the multivariate regression analysis (data not shown).

Taking into account the 11,124 hip fractures occurred in year 2011 in mainland Portugal, the total societal cost for the first year of treatment was estimated at €149 million. Direct medical costs, direct non-medical costal and indirect costs represent approximately 28.4%, 70.2% and 1.4% of this value respectively. This total value must be added to €66 million for the

second year of care. Altogether the cost of osteoporotic hip fractures can be estimated at approximately €216 million per year at current costs.

Mortality

Altogether, 50 (26.9%) of the 186 patients included in this study died within two years of suffering the hip fracture. Thirty-eight of the deaths occurred in the first year (mortality rate 20.4%) and 12 in the second (mortality rate of 8.1%: 12/148). Using Portuguese life tables (21), we estimated the expected yearly mortality for the general population, of similar age and gender composition, to be approximately 8.6%. Thus, our data demonstrates that an excess of mortality is observed in association with hip fracture within the first 12 months after the fracture, being nullified in the second year and, presumably, thereafter.

On this basis, we estimate that a total of 2,272 deaths will have occurred in Portugal following the 11,124 hip fractures observed in 2011, as opposed to the 962 expected in that population. Therefore, we conclude that probably around 1,310 excess deaths occur every year as a consequence of hip fractures.

The survival functions were not significantly influenced by either gender ($p = 0.47$), education (categorized in four levels, $p = 0.98$) or age (categorized in to three age groups $p = 0.15$), according to the log-rank test.

Quality of life

The mean pre-fracture HrQoL score was 0.65 (95% CI [0.63, 0.69]). Values for males and females were very similar to the reference for the Portuguese population of similar age [9] (0.68 vs 0.67 for men; 0.65 vs 0.56 for women).

One month after the fracture, the HrQoL decreased markedly to -0.18 (95% CI [-0,22, -0.15]). A two-sample paired student's t-test clearly rejected the hypothesis of equal HrQoL before and after the fracture ($p < 0.001$). One year after the fracture, patients partially recovered HrQoL, the average being, by then, 0.29 (95% CI [0.22, 0.36]).

Figure 1 shows health utility measured using the EQ5D before, one month after and one year after the hip fracture. On average, women report lower HrQoL scores than males but the differences observed did not reach statistical significance.

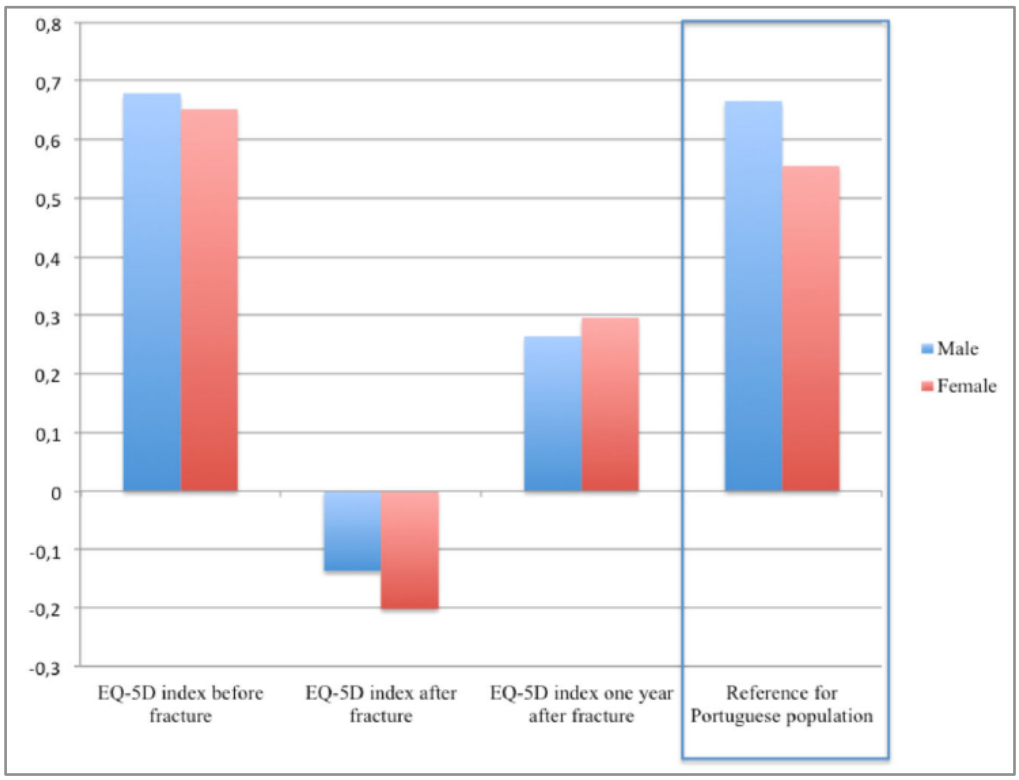

Figure 1.EQ-5D score before, one month after and one year after fracture, by gender, and the age matched references for the Portuguese population.

Factors influencing quality of life

We performed multivariate regression analysis to analyse whether short and long term relative losses and 1 year recovery of HrQoL,as defined in Table 2 of supplementary material), are associated with specific individual characteristics. Results are presented in Table 4. In all models the disturbances were found to be homoskedastic by the Breusch-Pagan / Cook-Weisberg test, and no multicollinearity problems were found.

None of the covariates included in the model demonstrated to be relevant in explaining the short term relative loss of HrQoL. Regarding long-term impact, the data shows that the covariates “age” and “level of education” have a statistically significant impact upon relative loss of HrQoL at 1 year after fracture. Age is associated with higher long-term relative loss. On the other hand, longer duration of formal education, is associated with a lower relative loss of HrQoL

The covariates age (-0.008) and being transferred to a long term care facility after the fracture (-0.471) were negatively associated with the 1 year recovery variable. Females, those with more years of education and those who received physiotherapy after fracture recovered, on average, more HrQoL one year after the fracture than their counterparts.

Table 4. Predictors of relative loss of HrQoL following hip fracture and its recovery.

	Short term relative loss		Long term relative loss		1 year recovery (Absolute values)	
	β	P value	β	P value	β	P value
Female	0.113	0.26	0.012	0.93	0.159	0.05*
Age	-0.001	0.93	0.019	0.03*	-0.008	0.05*
Married	0.101	0.40	-0.113	0.59	0.105	0.35
Level of education	0.001	0.98	-0.081	0.001*	0.024	0.04*
Living alone before	0.008	0.94	-0.127	0.54	-0.069	0.52
Nursing home before	0.097	0.57	-0.022	0.95	0.080	0.70
Physiotherapy	--	--	-0.001	0.54	0.002	0.01*
Living alone after	--	--	-0.229	0.21	0.236	0.02*
Nursing home after	--	--	0.390	0.06	-0.120	0.24
Long term care after	--	--	0.655	0.08	-0.477	0.01*
R-squared	0.02		0.17		0.25	

β, regression coefficient; * statistically significance

DISCUSSION

The objective of this investigation was to estimate the total annual cost of osteoporotic hip fractures to the Portuguese society, the per-patient costs and the impact of these fractures upon patients' HrQoL and life expectancy. We estimated that the total cost of the osteoporotic hip fractures in Portugal, in 2011, was nearly €216 million with a per-patient cost of €13,434 in the first year and €5,985 in the second year following fracture. Direct non-medical costs represent over 70% of the overall expenditure Indirect costs related with loss of productivity were marginal given the average age of the affected population. Higher age is associated with higher per-patient costs. This represents a very important burden upon the national health budget even if the absolute values are much lower than in northern European countries were both the incidence of fracture and their individual cost is much higher than in Portugal.[5 11 16 17]

Our results demonstrate that a hip fracture has a major impact on the individuals' HrQoL, which persists for at least one year. The EQ-5D scores were at baseline, in our sample, similar to the reference values for the age- and gender matched Portuguese population. The average HrQoL at 1 month after fracture was rated at levels equivalent to "worse than death". At one year there was considerable recovery of HrQoL but it still persisted significantly below baseline levels. The impact of HrQoL at 1 year is increased with increasing age and reduced in relation to higher levels of education.

Hip fractures in Portugal are associated with significant mortality: 26.9% of the victims had died within two years after fracture. This represents an excess of about 12% in observed versus expected mortality, which is observed almost exclusively in the first year after fracture. Altogether, we estimate that hip fractures observed in Portugal during the year 2011 were responsible for an excess of over 1,310 deaths. Excess mortality attributable to

fractures, and its cost, probably needs to be down-adjusted given that patients who sustain a hip fracture are, on average frailer than the general population. However, as there is no solid basis to quantify this adjustment, we decide to present absolute numbers and underline this potential limitation. On the other hand, given that the excess mortality occurs mostly on the first year it will tend to reduce other costs associated with care of the surviving patient with fracture.

To the best of our knowledge, this is the first study to collect individual level data regarding the cost of osteoporotic hip fractures in Portugal. The results confirm that hip fractures represent a relevant socioeconomic burden to the individual, family, health services and at society in Portugal.

Comparisons of results obtained with cost of illness studies should be made with caution, as both the reality under evaluation and the methodology employed can vary considerably.

The total societal cost of one hip fracture estimated by our study is similar to that reported for most other developed countries. For example, the per-patient fracture-related cost, per year, after a hip fracture was estimated at €16,379 in Netherlands in 2014,[17] €14,221 in Sweden, by 2006,[11] €13,205 in United States of America in 2013.[16] Reported costs in China are considerable lower: €3,177.[10] Discrepancies between these estimates seem to be essentially due to difference in costs per unit of care, rather than consumption of resources. It is quite possible that our total costs are underestimated by the use of the national tariff for services provided in the Portuguese NHS, which are commonly considered underpriced. On the other hand, we have considered costs that are frequently ignored by studies in this area, such as the cost of burial and of informal care. In support of this approach we would argue that death is associated with a direct cost of its own which should be appropriately considered as a non-medical direct cost. Similarly, the care provided by family and friends would have to be provided by someone in their absence and, therefore, represents a societal cost, even if it is endured by family and/or friends. We have only accounted for the costs of excessive number of deaths probably due to hip fractures (12%) and attributed to informal care the cost equivalent to our current national minimum wage: €505/month.

The percentage of patients undergoing treatment for osteoporosis with specific agents (16.7%) or with calcium plus Vitamin D (29.6%) after hip fracture is worryingly small. These percentages are, nevertheless, in line with international results[7 10 16 18] and emphasize the urgent need to strategies to improve the management of osteoporosis after fracture.

We identified that 17.8% of women and 20% of men living in the community at the time of fracture entered a long-term care facility, and that 18.5% of women and 25% of men were admitted to a nursing home during the first year after fracture. These values are in agreement with previous studies and demonstrate that loss of independence after hip fracture is a critical problem for these patients and for society.[19-21]

The results presented here support previous research demonstrating that hip fractures are associated with a substantial decrement in HrQoL.[11 22-24] In a systematic review, hip fractures were associated with a HrQoL decrement of approximately 50% shortly after fracture and 20% four months after fracture.[23] In our study, HrQoL values are close to the estimates found in others studies, with the exception of HrQoL one month after the event, which is remarkably lower in our case. This difference may be related to the exact time of evaluation, as HrQoL changes rapidly under these circumstances. Cultural issues may also play a role.[22]

Our results need to be viewed in the light of several positive aspects and also limitations. Among the positive aspects we underline the representative nature of our sample, derived not only from its size, but also the random selection strategy ensuring a valuable similarity between our sample with the overall population in terms of age, gender and geographic provenience. We have adopted statistical methodologies of analysis that are well rooted in the literature of COI studies. Our limitations include the retrospective collection of data, which may have some negative impact on the precision of the results, although several authors and consensus groups defend that personal health information can be collect with reasonable precision if specific and pre-defined questions are employed.[25 26] We have carefully respected the ten main recommendations published by Matt et al.[27] to ensure a good collection of data in retrospective studies.

Baseline HrQoL could have been especially open to this problem as patients might perceive their baseline HrQoL to be better than it actually was, which could lead to an overestimation of the loss of HrQoL due to the fracture. However, the HrQoL scores described by our participants before fracture were very similar to the reference for the Portuguese population.[9]

Our costs estimates may be underestimated for the use of national tariffs instead of market prices.

We opted to include all randomized patients even when the information could only be provided by a primary caregiver. Although this may be seen as a limitation, there is evidence that proxies can provide reliable information regarding EQ-5D scores[28 29] and resource utilization and costs of hip fractures,[30-32] when patients are not able or available to do so. We also verified in a regression model if the type of respondent (caregiver/patient) influence the costs and quality of life and this variable does not influence either costs or quality of life. Data not show.

CONCLUSION

The results of this study demonstrate that osteoporotic hip fractures represent an important cause of health resource consumption and overall societal cost in Portugal, despite its relatively low incidence in our country. Hip fractures have a marked negative effect on

HrQoL, which persists for at least one year and a significant impact on mortality. It is expected that the costs and societal impact of osteoporotic hip fractures will rise with the projected increase of life expectancy and the feminization of the elderly population.
Further research is needed to evaluate the cost-effectiveness of different strategies to prevent osteoporotic fractures and to limit their impact on the HrQoL and life expectancy of its victims.

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SUPPLEMENTARY MATERIAL

Costs per unit of each resource

It is usually accepted that unit costs should reflect the cost to society directly, and therefore, market prices should preferably be used.[12] However, in Portugal most health services, including the treatment of hip fractures, are provided under the umbrella of the National Health Service (NHS) As a result, true market prices are seldom found in the Portuguese context. The Portuguese Ministry of Health publishes every year, in the form of law, tariff lists for most of the medical services. In accordance, most of our unit prices come from those officially published tariffs lists. The unit cost of resources is presented in Table 1. The basis for the estimation of unit costs for services not provided within the NHS, is described on the observations column of that table.

For unit costs of productivity loss, national statistics on the cost of labour were used. Estimation of productivity losses due to hip fracture used the human capital approach. The monthly average national gross income for 2013 was taken from official published statistics. We performed two adjustments. The first, to consider the 23.75% of employers' contribution to social security schemes, the second to reflect the fact that in Portugal workers receive the equivalent to 14 monthly salaries per year. After these adjustments, the monthly average income of males and females was estimated at, respectively, €1,507.13 and €1,237.72.

Supplementary Table 1. Unit costs of resources and sources (all costs were computed at 2013 prices, in Euros).

Resource	Unit	Unit price (€)	Source	Observations
Rehabilitation care	Session	36,1	NHS official tariff (*)	
Inpatient care	Episode of inpatient care	2,500	NHS official tariff (*)	
Medical consultations	Consultation	31	NHS official tariff (*)	
Osteoporosis treatment	Annual cost	177.37 84	https://www.infarmed.pt/infomed/pesquisa.php	Osteoporosis treatment costs were calculated as an average of all osteoporotic treatments sold in 2011 in Portugal, multiplied according to posology for a one year treatment period, having in consideration weighted average prices provided for Infarmed (National Authority of Medicines and Health Products).
Diagnostic tests (X-rays/ Densitometry/ CTscan)	Unit	7,5/ 22,9/ 65	NHS official tariff (*)	
Nursing care	Hour	15	NHS official tariff (*)	
Long-term care	Day	87,6	NHS official tariff (**)	
Nursing home	Day	25,7	http://www.deco.proteste.pt/nt/nc/artigo/teste-saude-102-lares-de-idosos	No official data of reimbursement is available regarding nursing home costs. We used data from a national study published in 2012 by DECO (Portuguese consumer protection), which included 690 participants resident in nursing homes (public and private) and calculated the total cost according to the number of days.
Home care	Hour	4,38	Cost per hour of minimum national wage	
Technical aids	Unit	variable	Individual patients or care providers	The patients reported directly the costs of technical aids and home care alterations.
Informal care	Hour	4,38	Cost per hour of minimum national wage	The minimum national wage was €485 in 2013. To calculate the cost per hour we performed the adjustments made to estimate the unit costs of productivity loss. 40 hours of work per week was assumed.
Burial	Unit	1.257,66	http://www4.seg-social.pt/subsidio-por-morte	
Transportation	Km	0,51 per Km	NHS official tariff (***)	

(*) Diário da República. 1ª série- nº80-24 Abril 2013. (**) Portaria n.º220/2011 - Diário da República, 1.ª série — N.º 106 — 1 de Junho de 2011. (***) Diário da República, 2.ª série — N.º 108 — 4 de junho de 2012

Multivariate regression models for HRQoL

We specified 3 multiple regression models, each aimed at explaining the following dependent HrQoL variables: 1) the short-term relative loss of HrQoL, defined as the percent HrQoL loss comparing the status prior to facture and one month after fracture; 2) the long-term relative loss of HrQoL, defined as the defined as the percent HrQoL loss comparing the status prior to facture and one year after fracture and; 3) The recovery of patient's HrQoL, defined as difference between the patients' HrQoL measured one year after the facture and one month after the fracture.

The validity of the multiple linear regression model demands that a set of assumptions are verified.[33] The assumptions, homocedasticity and multicollinearity were investigated and found to be satisfied in all models of HrQoL (data not shown). As a consequence, we consider that the linear model is adequate and valid for the purposes of this study.

The covariates thought to influence HrQoL were divided into two groups. One first group reflects the individuals' demographic characteristics (age, gender, civil status, years of education and place of residence before the fracture). These covariates were included in all multivariate models. In addition, to explain some of the dependent variables, we used a second set of covariates meant to reflect the place of residence after the fracture – whether the patient went to a long-term care facility or to a nursing home. To assess the importance of physiotherapy on the patients' recovery, we also included a covariate to reflect the utilization of this type of medical care after the hip fracture. Table 2 presents the definition of all variables, both dependent and independent used in the regression models.

Supplementary Table 2. Definition of variables, both dependent and independent, used in the regression models

Variable	Definition
	Dependent variables
Short term HrQoL relative loss	Percent HrQoL loss comparing the status prior to facture and one month after fracture
Long term HrQoL relative loss	Percent HrQoL loss comparing the status prior to facture and one year after fracture
1 year Recovery	Difference between the patients' HrQoL measured one year after the facture and one month after the fracture
	Covariates
Female	= 1 if gender is the individual is female
Age	Age of the individual
Married	= 1 if the individual is married
Level of education	Number of years of school education
Living alone before	= 1 if the individual resided alone before the fracture
Nursing home before	= 1 if the individual resided in a nursing home before the fracture
Physiotherapy	Number of sessions of physiotherapy in the year after the fracture
Nursing home after	= 1 if the individual went to a nursing home after the fracture
Long term care after	= 1 if the individual used a long-term care facility after the fracture
Living alone after	= 1 if the individual resided alone after the fracture

Chapter 6

COST-EFFECTIVENESS OF INTERVENTION THRESHOLDS FOR THE TREATMENT OF OSTEOPOROSIS BASED ON FRAX® IN PORTUGAL

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Marques A, Lourenço O, Ortsäter G, Borgström F, Kanis, JA, da Silva JAP. Cost-effectiveness of intervention thresholds for the treatment of osteoporosis based on FRAX® in Portugal. Calcif Tissue Int 2016;99(2):131-41.

ABSTRACT

Introduction

The aim of the present study was to identify the 10-year probabilities of a major and hip osteoporotic fracture probabilities using FRAX® validated for Portugal, above which pharmacologic interventions become cost effective in the Portuguese context.

Methods

A previously developed and validated state transition Markov cohort model was populated with epidemiologic, economic and quality-of-life fracture data from Portugal. Cost-effectiveness of FRAX®-based intervention thresholds were calculated for generic alendronate and proprietary zoledronic acid, denosumab and teriparatide were compared to "no intervention", assuming a willingness to pay of €32,000 (2 times national Gross Domestic Product per capita) per QALY (Quality-Adjusted Life Years).

Results

In the Portuguese epidemiological and economic context, treatment with generic alendronate was cost-effective for men and women aged 50 years or more, with 10-year probabilities at or above 8.8% for major osteoporotic fractures and 2.5% for hip fractures. Cost-effective threshold 10-year probabilities for major osteoporotic and hip fractures were higher for zoledronic acid to (20.4% and 10.1%), denosumab (34.9% and 10.1%), and teriparatide (77.8% and 62.6%), respectively.

A tool is provided to perform the calculation of cost-effective intervention thresholds for different medications, according to age group and diverse levels of willingness to pay (WTP).

Conclusions

Cost-effective intervention thresholds, for different medications, age-groups and WTP, based on 10-year probabilities of major and hip fracture probabilities calculated with FRAX® are provided.

INTRODUCTION

Osteoporosis is an asymptomatic, progressive skeletal disease characterized by porous and weak bones leading to an increased rate of fractures.[1] Morbidity, mortality and costs of osteoporosis and associated fractures are already one of the most important burdens faced by health-care systems in Europe and is set to increase in the near future.[2] In this context, cost-effectiveness evaluations of treatments important to inform the judicious selection of intervention strategies.

Ideally, decisions on treatment should be based on their impact quality of life while taking the cost into account. In a population perspective the cost-effectiveness of an intervention will be higher when the prevalence of the event is higher: more people are exposed to adverse events and more resources are exhausted for fewer benefits. Decisions to prevent fracture should, therefore, be based on the absolute risk.

This has become possible since the development of FRAX®[3] and a computer-based algorithm that provides an estimate of the probability of hip fracture and major fractures (spine, hip, forearm or humerus) in men and women over the subsequent ten years, based on clinical risk factors (CRFs) with or without bone mineral density. This estimate allows the identification of high-risk individuals as preferential candidates for pharmacologic intervention.[4] It can also be incorporated into cost-effectiveness analyses, the results of which can inform intervention guidelines in a societal perspective. [5 6]

Given the large variation in the epidemiology and economic burden of osteoporotic fractures, as well as the economic resources available and willingness to pay, cost-effective intervention thresholds based on FRAX® need to be country-specific. This strategy has already been adopted, in the UK,[7] US,[8] Switzerland[9] and Greece.[10] FRAX® has been calibrated to the Portuguese epidemiological context and made available – FRAX®-Port[11] Recent national studies proving population reference values for quality of life[12] and data on the impact of hip fractures in terms of costs, quality of life and mortality[13] have laid the ground to promote this important development in Portugal.

The aim of the present study was to identify the FRAX®-based 10-year probabilities of major and hip fractures above which pharmacologic interventions became cost effective in the Portuguese setting of fracture incidence, morbidity, mortality and management strategies, as well as overall mortality rates, cost of interventions and willingness to pay.

METHODS

The analysis was performed from a societal perspective, i.e. both direct and indirect costs were included. Costs of excess of mortality related to hip fractures when compared to the gender and age-matched general population were also considered.[13]

The cost-effectiveness of generic alendronate and proprietary zoledronic acid, denosumab and teriparatide were compared to "no intervention", by simulating costs and outcomes in a cohort of persons aged 50 years or older, at different levels of osteoporotic fracture risk. These four treatment options were selected to represent the diversity of intervention strategies currently available in Portugal, in terms of mechanism of action and cost.

Health benefits of outcomes (effectiveness) were measured as quality-adjusted life years (QALYs) gained, and the results were presented as the incremental cost-effectiveness ratio (ICER).

Model

A Markov cohort simulation model, previously developed and validated, was used to estimate the cost-effectiveness of interventions based on the FRAX® model for Portugal (for detail see refs[4 9 14-16]). The model consisted of the following health states: well, hip fracture, vertebral fracture, forearm fracture, and other fracture, post-hip fracture, post-vertebral fracture and death. A patient started the model simulation in the Well/No event state and passed through the model in 6-monthly cycles: The model took a lifetime perspective.

After 6 months in any fracture state, the patient had a risk of sustaining a new fracture or dying. After 12 months, the patient moved to the corresponding post-fracture state if no additional event had occurred. The patient automatically remained in the post fracture state if he did not die or sustained a new hip or vertebral fracture. Only the event with the highest mortality, cost and quality of life reduction was accounted for at any given time interval. We did not differentiate men from women in this analysis because, according to our economic evaluation,[13] the input data (costs, treatment effect, mortality increase) are similar between genders. The gender differences in risk of fracture are incorporated as part of FRAX®, in the risk estimate

Costs

Direct and indirect costs associated with hip fragility fractures, at 2013 price levels, were derived from an empirical study in Portugal.[13] Costs associated with medications and with selected units of care are presented in Table 1.

Table 1. Summary of costs per unit of care and QoL multipliers

Unit costs (€)		Drug Costs /year (€)		QoL multipliers	
BMD measurement	22.9	Generic alendronate	98.88	Hip fractures 1st year	0.47
Nurse Visit	15.0	Denosumab	552	Clinical vertebral fracture 1st year	0.649
Physician visit	31.0	Teriparatide	4,234	Forearm fracture 1st year	0.934
Lab testing	41.23	Zoledronic acid	347.24	Other fractures 1st year	0.902
Cost of IV Injection	20.20	Generic proton pump inhibitor	12.00=1 month	--	--

It was assumed that the unit cost for medications and for other aspects of care involved in treating fractures would be the same regardless of age, race, or gender. Annual drug costs varied from € 98.88 to €4,234. Those receiving treatment were assumed to have an additional physician visit each year (at €31 each) and to incur the cost of a BMD test (€22.9) every 2 years. In addition, nurse visits (€15.0) were assumed as required every 6 months for denosumab, every year for zoledronic acid and only once for teriparatide. The cost of IV injection (€20.20) was added as appropriate. A limited laboratory monitoring was assumed to take place at the beginning of each treatment and every year subsequently for all treatments (€41.23).

Gastrointestinal complications were assumed to be side effects of generic alendronate.[17] These were estimated to lead to 23.5 additional GP consultations per 1,000 patient-months in the initial treatment period and 3.5 thereafter, and to require the use of a generic proton pump inhibitor for one month per event, at a total cost of 12€ per treatment in Portugal. No other side effects were considered.

Incidence, mortality and costs of fractures according to age

The incidence and costs of hip fractures were taken from Marques et al.[11 13] As vertebral, forearm, and other fractures are inconsistently reported in Portugal,[11 18] the incidence and cost of clinical vertebral fractures, forearm and other fractures was calculated by assuming that the ratio of these fractures to hip fracture would be similar in Portugal as compared to Sweden[15 19] (Table 2). A similar methodology has been adopted in other published studies.[9 11 20]

The age-specific mortality rates for the general population in Portugal were based on the 2011 data provided by Instituto Nacional de Estatística – INE (Portuguese Statistics Institute[i])

[i] Document can be downloaded at https://www.google.pt/url?sa=t&rct=j&q=&esrc=s&source=web&cd=5&ved=0CDkQFjAE&url=https%3A%2F%2Fwww.ine.pt%2Fngt_server%2Fattachfileu.jsp%3Flook_parentBoui%3D217825026%26att_display%3Dn%26att_download%3Dy&ei=rRxwVaWVA4T8UoT-gsAL&usg=AFQjCNF425t1t09yNBr9DzzHU9gL_q5DXQ. Accessed 4 June 2015.

(data not shown). The increase in mortality after hip, clinical vertebral and other fractures was derived from [21] and [22] (data not shown).

Table 2. Average annual hip fracture incidence per 100,000 inhabitants, 2006-2010 and cost per fracture, by age-group in Portugal, 2013 [11 13]

Age	Annual incidence per 100 000				Fracture related costs (€)			
	Hip fracture	Clinical vertebral fracture	Forearm fracture	Other fractures	Hip fracture	Clinical vertebral fracture	Forearm fracture	Other fractures
50-54	19	49	128	139	8,780	1,581	1,854	3,196
55-59	30	74	197	225	8,780	1,581	1,854	3,445
60-64	52	82	155	167	8,780	1,581	1,854	4,101
65-69	99	140	212	247	10,969	10,533	1,854	6,825
70-74	207	262	302	508	10,969	10,533	1,854	6,639
75-79	434	353	340	839	13,530	10,903	1,854	6,604
80-84	927	499	496	1518	13,530	10,903	1,854	6,221
85-89	1723	763	643	2784	15,179	10,977	1,854	6,745
90+	2353	923	648	2847	15,179	10,977	1,854	6,745

Treatment efficacy

This study evaluated treatments on the basis that they will be typically given for 5 years, as in other studies,[8-10 14-16 23] with the exception of teriparatide, where a 18 months of treatment was predicted, as clinically recommended.[24] After stopping treatment, risk reduction was assumed to reverse in a linear manner over 5 years as is generally assumed in health economic analyses with bisphosphonates[25] or denosumab [16] and two years for teriparatide.[24]

The model also incorporates incomplete adherence to therapy as seen in clinical practice, thus reducing the number of avoided fractures, and consequently QALYs gained for the target population as a whole. In this study, the dropout rates for alendronate and denosumab were based on the study of Freemantle et al.[26] and has been used previously.[16] Drop-out rate for zoledronate and teriparatide were assumed equal that of denosumab, taking into account the different time points of administration (information regarding the different dropouts rates can be found in supplementary Table 1).

Efficacies for alendronate,[17] zoledronic acid,[27] denosumab[28] and teriparatide[24] on fracture risk were taken from meta-analysis or randomized controlled trials (for more detail, see supplementary Table 1).

Utilities

Published age-specific reference data for quality of life (QoL) in the normal Portuguese population were used.[12] These were based on the EuroQoL EQ-5D questionnaire,

encompassing the health dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Data on fracture related loss of QoL at 1 and 2 years after hip fracture, based on the same instrument, were collected from a Portuguese study.[13] The effects of vertebral, forearm, and other fractures on QoL was based on Swedish data[29 30] as no reliable data are available for Portugal. A similar methodology has been adopted in other published studies.[9 11 20] The multipliers to convey the impact of fractures on quality of life are presented in Table 1.

Intervention thresholds

Using the Markov cohort simulation model mentioned above, we computed the relationship between the estimated 10-year fracture probabilities, for hip and major fractures separately, and the cost (€) per QALY gained (incremental cost-effectiveness ratio – ICER) (for all possible combinations of clinical risk factors (prior fragility fracture, age and sex, body mass index, prior use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis, a parental history of hip fracture, current cigarette, smoking, and alcohol intake of 3 or more units/day) between ages 50 to 85 years in 5-year increments and BMD T-scores between −1.5 and −3.5 SD (0.5 increments). In the model, the individual's body mass index was set to 25 kg/m^2. This strategy yielded a total of 2,558 scenarios of 10-year fracture probabilities and ICERs, one for each possible combination. As an example, Figure 1 illustrates the relationship between the absolute 10-year fracture probability and the cost (€) per QALY gained, for all combinations, using generic alendronate as the treatment option. The figure displays a non-linear and decreasing relationship between the 10-year year hip fracture probability and the cost (€) per QALY gained.

To estimate the intervention thresholds (ITs) we began by fitting a curve to the data, and deriving the analytical expression that represents the non-linear relationship between the two variables. Figure 1 in supplementary material depicts the mathematical function (curved black line) that best represents the statistical relationship between the absolute 10-year fracture risk and ICER, without controlling for age. The curve fitting was performed using regression models based on fractional polynomials functions, a methodology particularly suited to providing concise and accurate formulae to represent such non-linear relationships.[31 32] In agreement with Royston and Altman[31] we limited the function to polynomials of a maximum degree of two. Curves were fitted for 10-year probability estimates of hip and major fracture for each treatment considered (generic alendronate, zoledronic acid, denosumab, and teriparatde), for each age group (50-85), and for the whole population. In total, 72 curves were fitted (more details can be found in supplementary material).

Willingness to pay

Deciding if one intervention is cost-effective or establishing intervention thresholds based on cost-effectiveness requires the consideration of a maximum acceptable cost per utility gained. The "decision" is based on the comparison between the ICER, i.e. the cost per QALY gained with that intervention and a pre-set value of what society is willing to pay per QALY: the so-called cost-effectiveness threshold.[33]

However, there is no generally accepted or recommended cost effectiveness threshold for medical interventions in Portugal. We, therefore, used as reference a WTP of two times the gross domestic product (GDP) per capita.[29 34] This figure has been previously adopted in similar studies.[9 10 29] The 2014 GDP per capita in Portugal was approximately 16.400€ [35] and, thus, we adopted a WTP of €32,000.00 in the present study. In addition, to illustrate for different cost-effectiveness thresholds and their impact on decisions, we also estimated the intervention thresholds for a WTP of €20,000.00 which is close to the value suggest by NICE in 2015 for new treatments and technologies.[36]

Given the lack of rigid guidance on the WTP that should be adopted, we provided a simple tool that allows the calculations of the cost-effective intervention threshold based on FRAX®-Port for different age-groups and interventions at a WTP of the user's choice. This can be found at https://dl.dropboxusercontent.com/u/4287154/OsteoThre/Thresh_computationPortugalV001.xlsm.

We report the main findings with a base case analysis of individuals age 65 years-old person, with a T-score of -2.5 and a previous fracture as the only risk factor. We report the incremental cost effectiveness ratios (ICER) of intervention with a specific drug vs no intervention.

RESULTS

Table 3 summarises the base-case analysis of cost-effectiveness of the different treatments compared with no treatment. The last two rows of Table 3 present the incremental cost-effectiveness ratios (ICER).

All the drug intervention alternatives produce better health outcomes, as measured by several indicators, when compared with "no treatment". In this particular example, the model estimates that intervention with generic alendronate would avoid 2 hip fractures per 1,000 treated patients over a ten year period, whereas intervention with denosumab would avoid 4 fractures. The outcome of interventions is also better than no intervention in terms of Life years and QALYs gained. These health outcomes results mirror the known clinical efficacy of the different treatments considered. The incremental costs calculated show that all treatment alternatives are more costly than no treatment for the particular patient represented in this

table. For example, on average, treating patients such as this with generic alendronate will cost €153,00 more, than those with no treatment – this is the cost paid for preventing those two hip and three vertebral fractures and gaining 0.0056 QALYs. The incremental cost per QALY gained (ICER) for treating a patient as that exemplified in Table 3 with generic alendronate vs no treating is €27.370,00 (153/0.00559). Depending on the WTP adopted, this will or will not be considered to be cost-effective.

The cost of the drug used has a decisive impact on the incremental cost of intervention vs no intervention, as exemplified by the incremental cost of teriparatide.

Table 3. Base-case analysis for incremental cost-effectiveness (cost per life year and per QALY gained).

	Alendronate vs. no treatment	Zoledronate vs. no treatment	Denosumab vs. no treatment	Teriparatide vs. no treatment
Cost per patient				
Morbidity cost difference	-73	-192	-161	-119
Treatment cost difference	227	1,368	1669	5,325
Incremental cost	153	1,176	1,508	5,206
Avoided fractures during 10 years / 1,000 patients				
Hip fractures	-2	-4	-4	-2
Vertebral fractures	-3	-10	-8	-4
NNT to avoid 1 hip fracture	499	227	244	426
NNT to avoid 1 vertebral fracture	355	99	118	280
QALYs and life years/patient				
Life years gained (undiscounted)	0.00662	0.020	0.017	0.010
Life years gained (discounted)	0.00409	0.012	0.010	0.006
QALYs gained	0.00559	0.017	0.014	0.009
Cost/life year gained	37,442	96,006	176,891	868,275
Cost per QALY gained (ICER)	27,370	70,071	128,503	600,070

Illustration based on a 65 year-old person, with a T-score of -2.5 and a previous fracture as their only risk factor.

NNT - number needed to treat.

Figure 1 presents the scatter plot of the relationship between the 10-year probability of a major osteoporotic (A) or hip fracture (B) with the cost per QALY gained with generic alendronate vs no treatment. In both figures the cost per QALY reduces as the probability of fracture increases, the decline being more marked at the lower risk ranges. The cost per QALY, for a given 10-year fracture risk has a strong trend to reduce as age increases. The results show that drug intervention with generic alendronate was a cost-effective alternative to no treatment at a 10-year major fracture probability of 12.3 and 8.8% for WTP of €20,000 and €32,000, respectively. This figure also shows that at 10-year major fracture probabilities of 25% or higher, drug intervention with generic alendronate is a “dominant” alternative, meaning that it delivers better health outcomes at lower costs when compared with no-treatment.

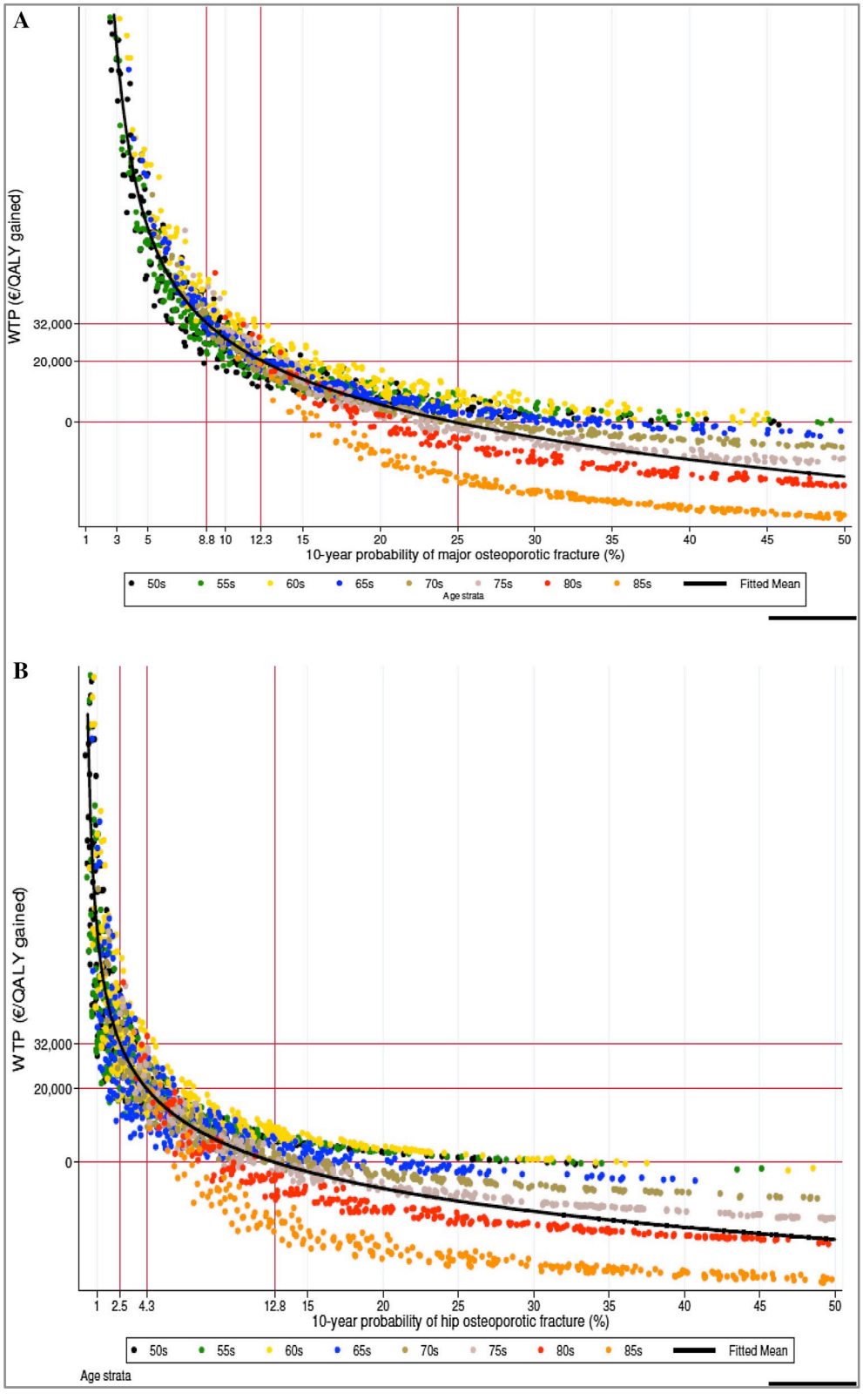

Figure 1. Relationship between absolute 10-year probability of major fracture (a) or hip fracture (b) and the cost per QALY gained, for generic alendronate versus no treatment.

Colors identify different age groups. The horizontal lines represent WTP of €0, €20,000 and €32,000 and the vertical lines mark the corresponding cost-effectiveness thresholds.

Table 4 shows estimated cost-effectiveness thresholds for intervention with each of the active agents considered vs no treatment, for WTPs of €20,000 and €32,000. The 10-year major osteoporotic and hip fracture probability at which treatment is cost-effective was relatively stable across all ages, in both sexes. The 10-year probability of osteoporotic fracture above which intervening with alendronate becomes cost-effective vs no treatment, irrespective of age ("all ages"), for a WTP = €32,000.00, was 8.8% for major fractures and 2.5% for hip fractures.

The intervention threshold for "all ages" was derived from running the model for the whole population. Thus, this value is not the arithmetic mean of the individual five-year- age groups.

The level of fracture risk "required" to make an intervention cost-effective was markedly affected by the cost of medication, as expected. Compared to this factor, the impact of the WTP was much small.

Table 4. Cost-effective intervention thresholds expressed as the 10-year probability of major or hip fracture (%) for the different interventions, vs no treatment, according to age, at WTP of €20,000.00 and €32,000.00

Age	10-year probability of a major fracture (%)				10-year probability of a hip fracture (%)			
	Generic alendronate vs no treatment	Zoledronic acid vs no treatment	Denosumab vs no treatment	Teripartide vs no treatment	Generic alendronate vs no treatment	Zoledronic acid vs no treatment	Denosumab vs no treatment	Teripartide vs no treatment
				WTP= 32,000.00€				
50	8.6	16.7	22.5	37.1	2.6	9.5	15.5	35.6
55	8.7	17.8	24.7	30.9	2.4	8.6	14.5	21.2
60	10.4	23.2	33.7	63.8	3.0	11.9	20.7	47.8
65	9.2	20.5	31.2	60.8	2.3	8.8	16.4	39.8
70	8.6	21.0	33.0	60.0	2.3	10.5	20.9	47.1
75	8.1	22.9	38.7	76.3	2.1	12.3	27.1	63.3
80	7.1	21.8	39.6	84.3	1.7	11.4	27.9	69.7
85	5.9	18.6	36.9	71.3	1.3	9.0	25.9	60.6
All	**8.8**	**20.4**	**34.9**	**77.8**	**2.5**	**10.1**	**22.6**	**62.6**
				WTP= 20,000.00€				
50	11.8	21.5	26.5	39.1	4.7	14.5	20.1	38.3
55	12.1	23.0	29.3	32.4	4.2	13.1	18.8	22.8
60	15.4	31.1	40.4	68.4	5.9	18.5	27.0	51.4
65	13.0	27.1	37.3	65.0	4.1	13.4	21.3	42.9
70	11.9	27.8	39.5	64.1	4.0	16.2	27.3	50.7
75	10.9	30.6	46.5	82.4	3.6	19.1	35.5	68.2
80	9.3	29.0	47.6	91.3	2.7	17.6	36.6	75.1
85	7.4	24.3	44.3	76.8	1.8	13.8	33.9	65.3
All	**12.3**	**27.6**	**43**	**85**	**4.3**	**15.8**	**30.9**	**68.7**

DISCUSSION

Both from the health economics and the clinical viewpoint, it is appropriate that treatment decisions on osteoporosis are based on the absolute risk of fracture as opposed to the consideration of relative risks and the impact of individual risk factors.[3 37-39] Only with absolute risks of fracture and the quantified consideration of the effectiveness of interventions can the practicing clinician estimate the true value of an intervention, and thus, its indication. However, the number of countries where guidelines for treatment are based on cost-effectiveness thresholds is still very limited. The development of FRAX® and its adaptation to the Portuguese population FRAX®-Port made this possible in this country, as it provides the 10-year probability fracture integrating not only fracture hazards, but also the actual national epidemiology of fractures and of competing death hazards.[40]

Considering the costs of interventions adds a dimension of social responsibility to medical decisions, which is especially important in countries and instances where the cost of care is partially or totally supported by public resources, as in Portugal. The use of comprehensive and fully validated economic models to estimate cost-effectiveness will help reassure those health professionals that are reluctant to allow costs as drivers of medical decisions: once costs are computed as ICER (i.e., cost per QALY gained), the actual impact of the intervention upon quality and duration of life, i.e. its actual value, becomes a decisive part of the equation.

This strategy has already been adopted in the UK,[7] US,[8] Switzerland[9] where, respectively, a probability for a major osteoporotic fracture of 7%, 20%, 13.8% was considered as a cost-effective intervention threshold for generic alendronate. Following a similar strategy for Greece[10], a value of 10% is proposed for people under the age of 75 years and 15% for those above. All factors that are relevant in the establishment of intervention thresholds, from the epidemiology of fracture and death, to the costs of interventions and WTP, can vary markedly between countries. It is, therefore, appropriate that cost-effectiveness studies are replicated nationally. We have based our calculations on data recently collected purposely in our population. The only exception lies in the incidence and costs of non-hip fractures, which were extrapolated from data collected in Sweden. The economic model employed has been developed, validated and field-tested several times by experienced researchers in the field, who took an active role in designing the data collection and analysis for this study. For all, these reasons we are confident that the results presented herein have a high degree of validity.

The present study confirms that the 10-year probability of fractures estimated by FRAX® provide a sound basis on which to establish cost-effectiveness thresholds, given its strong

negative correlation with cost per QALY gained with all active interventions. This cost is unacceptably high at the very low risks of fracture but diminishes rapidly to achieve levels compatible with cost-effectiveness in the range of 6 to 10% risk for major and 1.3 to 3% risk of hip fracture over the subsequent 10 years. These are probabilities that most clinicians will consider as warranting preventive intervention, even in the absence of formal evaluation of cost-effectiveness. Such observations support the face validity of the results and may, thus, contribute to their acceptance and potential impact on practice.

Age affects the cost-effectiveness of interventions. In general, the cost-effective intervention thresholds diminish with age from 60 years onwards for both the bisphosphonates tested. This relationship is less uniform with denosumab and teriparatide. This age-dependent variation of intervention-thresholds is within a range of 30-40% above and below the estimated value for all ages, which may allow consideration of the latter value for all ages. The interested professional may always refer to data in table 4 to consider the precise intervention threshold for a given age group.

Our study indicates that generic alendronate, the most affordable intervention, is a cost effective intervention, at a WTP of €32,0000, for women and men whose FRAX®-Port estimated 10-year probability of fracture equal or superior to 8.8% for major fractures and/or equal or superior to 2.5% for hip fracture.

As expected, the cost of medication has a marked impact upon cost-effective intervention thresholds, as the fracture prevention efficiency is not proportional to cost. According to our results, teriparatide only becomes cost-effective for FRAX®-Port risk estimates above 77.8% for major osteoporotic fracture and 62.6% for hip fractures. These results are consistent with the current restriction of this medication, in clinical practice, to patients with especially severe and resistant osteoporosis. In such cases, clinical judgment may justifiably overcome the cost-effectiveness evaluation. In the case that medications other than bisphosphonates become necessary, due to intolerance, for instance, we would endorse the view, also supported by several other authors, that the alternative treatment should be considered even if the corresponding intervention threshold has not been reached.[6 7 9 10 41 42]

Compliance also deserves consideration when comparing the four treatments. Oral bisphosphonates have been associated with poor long-term compliance,[43 44] which will decrease health outcomes and decrease the cost-effectiveness of drug therapy.[45] Similar considerations may apply to poor absorption of these agents due to lack of adherence to advice regarding drug administration. Parenteral agents overcome both these limitations.

The value set as willingness to pay has an obviously decisive impact on the cost-effective threshold thresholds. As resources available to pay for interventions diminish, treatment must be limited to those instances where the gain per cost is higher and thus, less people will have

access to treatment. Considering a WTP of € 20,000 as opposed to 32,000 in our model increases the cut-offs for intervention with underlines the validity and robustness of the strategy used. Given the absence of an official WTP in Portugal, individual physicians and professional bodies and endowed with a certain degree of freedom in considering different values per QALY, as a basis for their decision. They are not obliged to adhere to either the €32,000 or the €20,000 cut-offs we explore in this paper. For this reason, a tool allowing the calculation of cost-effective thresholds for different ages and medications, with freedom in the choice of WTP and age group is provided to interested readers.

Because cost-effective intervention thresholds are dependent on the incidence, mortality and morbidity of fractures as well as on the costs and frequency of use of medication and other treatment modalities, the results of this study are not necessarily applicable to other countries and results obtained in different countries are difficult to compare.

Despite this, it is interesting to see that in the different European countries were such studies have been performed, the probabilities of major fractures selected as making generic alendronate a cost-effective intervention are quite similar: 7% in UK,[7] 8.8% Portugal, 13.8% Switzerland[9] and 10% to 15%, depending on age, in Greece.[10] This is quite remarkable given the disparities in the clinical and economical epidemiology of factures and, especially, the WTP adopted for each country: UK €27,786.00, Switzerland €115,000.00, Portugal €32,000.00 and Greece €30,000.00.

Some limitations of this study need to be considered. The incidence and costs of clinical vertebral fracture, forearm and other fractures was calculated by assuming that the age and sex-specific ratio of these fractures to hip fractures would be similar in the Portugal as in Sweden. The assumption has been tested in several countries.[46] The economic costs of fractures and their impact on quality of life was based on a retrospective collection of data, with the inherent limitations of this methodology. The model, despite its extensive external validation, rests upon a series of assumptions, including the expected patterns of resource use. Drug efficiency is estimated on the basis of randomized clinical trials, which may not exactly reflect clinical practice. Other possible limitation is due the reversibility of denosumab and teriparatide after 5 and 2 years of therapy as the treatment effect over 10 years may differ from the treatment with bisphosphonates.

Despite these limitations, the study is based on very robust evidence, mostly collected in the population of interest, and qualified methodology, thus providing results that should not differ significantly from reality. This information will be included in Portuguese national guidelines and will hopefully be of assistance to individual clinicians, scientific bodies as well as to health-policy makers by providing a more efficient use of human and financial resources in

the combat to the ever-growing epidemics of osteoporotic fractures. The Portuguese guidelines on when to start medication for osteoporosis will be based on FRAX® cost-effectiveness intervention thresholds, but consideration shall also be given to circumstances which may justify individually tailored decisions, such as treatment at lower risk-estimates, or adoption of more costly medications due to intolerance or contra-indication to alternatives.

Cautious inferences may also be made for other countries with similar incidence and costs of fractures.

CONCLUSIONS

Cost effective intervention thresholds based on 10-year probabilities of major and hip fracture probabilities calculated with FRAX®-Port are provided. These thresholds vary according to age willingness to pay and, most especially, the cost of medication used.

Treatment with generic alendronate is cost-effective for people aged 50 or more years, with a 10-year probability of fracture (FRAX®-Port) at or above 8.8% for major osteoporotic fractures and 2.5% for hip fracture, at willingness to pay of €32,000 per QALY. At probabilities for major fractures above 25%, this medication will actually save money in comparison to no intervention.

Using these thresholds when making decisions on whether to treat will greatly increase the efficiency in the use of heath resources to prevent osteoporotic fractures in Portugal.

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SUPPLEMENTARY MATERIAL

The analytical expression that best describes the relationship between the 10-year fracture probability and the ICER, takes the form of the following equation:

$$ICER = \xi_0 + \xi_1 pr^{(p_1)} + \xi_2 pr^{(p_2)}$$

where $\xi_i \; i = 0,1,2$ are the coefficients of the fractional polynomial, *pr* represents the 10-year fracture probability (either hip or major) and (p_1) and (p_2) are real-valued powers of the polynomial. Using the terminology of fractional polynomial regression $pr^{(0)} = \ln(pr)$. For example, the analytical expression of the curve depicted in

Supplementary Figure 1 is given by

$$ICER = 76222{,}9 + 630725{,}8\, pr^{(-2)} - 24015{,}1\, pr^{(0)}$$

which is equivalent to

$$ICER = 76222{,}9 + \frac{630725{,}8}{pr^2} - 24015{,}1 \ln(pr)$$

Supplementary Table II displays the coefficients and powers for all cases considered in the analysis. After fitting all curves, finding the intervention threshold, for a given Willingness To Pay - WTP_0, involves solely solving, in *pr*, the equation

$$WTP_0 = 76222{,}9 + \frac{630725{,}8}{pr^2} - 24015{,}1 \ln(pr)$$

Let us assume that the solution of the equation is *pr**. Because the curve that represents the relationship between the 10-year probability of fracture and the ICER is monotonic decreasing, for 10-year fracture probabilities above *pr**, the treatment can be considered cost-effective for WTP equal to WTP0, and the opposite for 10-year fracture probabilities below pr*.

Supplementary Table 1. Dropout incidence by year and efficacy of different treatments

		Alendronate	Zoledronate	Denosumab	Teriparatide
	Dropout incidence (%)				
Time point	after 0.5	37.2	0.0	20.1	0.0
	1	26.1	31.4	14.1	31.4
	1.5	22.4	0.0	12.1	0.0
	2	19.8	21.5	10.7	0.0
	2.5	20.5	0.0	11.1	0.0
	3	30.3	25.6	16.4	0.0
	3.5 and ongoing	0.0	0.0	0.0	0.0
	Efficacy in fractures treatment (0-1)				
Type of fractures	Hip Fracture	0.62	0.59	0.60	0.47
	Vertebral Fracture	0.56	0.23	0.32	0.35
	Other Fractures	0.81	0.75	0.80	0.47
	Wrist Fractures	0.67	0.75	0.85	0.47

Supplementary Table 2. Coefficients and powers for all cases considered in the analysis

	Major Fractures						Hip Fractures				
Age	**psi0**	**psi1**	**psi2**	**(p1)**	**(p2)**	**Age**	**psi0**	**psi1**	**psi2**	**(p1)**	**(p2)**
Generic alendronate						**Generic alendronate**					
50	-35411.7	450092.8	179218.0	-2	-0.5	**50**	28016.3	34457.4	-9864.3	-1	0
55	-34521.7	450092.8	179218.0	-2	-0.5	**55**	25954.8	34457.4	-9864.3	-1	0
60	-27619.1	450092.8	179218.0	-2	-0.5	**60**	31611.5	34457.4	-9864.3	-1	0
65	-32342.4	450092.8	179218.0	-2	-0.5	**65**	25621.5	34457.4	-9864.3	-1	0
70	-35022.3	450092.8	179218.0	-2	-0.5	**70**	25262.0	34457.4	-9864.3	-1	0
75	-37964.9	450092.8	179218.0	-2	-0.5	**75**	22840.0	34457.4	-9864.3	-1	0
80	-43896.6	450092.8	179218.0	-2	-0.5	**80**	16951.9	34457.4	-9864.3	-1	0
85	-54375.8	450092.8	179218.0	-2	-0.5	**85**	6774.0	34457.4	-9864.3	-1	0
All	76222.9	630725.8	-24015.1	-2	0	**All**	33384.6	29790.5	-13983.5	-1	0
Zolendronic Acid						**Zolendronic Acid**					
50	27385.1	588574.9	-7489.8	-1	0.5	**50**	83159.5	39863.1	-24616.2	-1	0
55	30405.9	588574.9	-7489.8	-1	0.5	**55**	80307.0	39863.1	-24616.2	-1	0
60	42784.2	588574.9	-7489.8	-1	0.5	**60**	89603.3	39863.1	-24616.2	-1	0
65	37277.1	588574.9	-7489.8	-1	0.5	**65**	80989.6	39863.1	-24616.2	-1	0
70	38257.4	588574.9	-7489.8	-1	0.5	**70**	86068.9	39863.1	-24616.2	-1	0
75	42156.5	588574.9	-7489.8	-1	0.5	**75**	90505.5	39863.1	-24616.2	-1	0
80	40028.4	588574.9	-7489.8	-1	0.5	**80**	88309.4	39863.1	-24616.2	-1	0
85	32768.6	588574.9	-7489.8	-1	0.5	**85**	81810.5	39863.1	-24616.2	-1	0
All	13610.9	611635.5	-571.3	-1	1	**All**	83171.1	40033.2	-23800.2	-1	0
Denosumab						**Denosumab**					
50	46797.5	1024379.0	-12701.4	-1	0.5	**50**	143124.3	71682.1	-42250.9	-1	0
55	53732.0	1024379.0	-12701.4	-1	0.5	**55**	140071.3	71682.1	-42250.9	-1	0
60	75422.7	1024379.0	-12701.4	-1	0.5	**60**	156594.8	71682.1	-42250.9	-1	0
65	70022.7	1024379.0	-12701.4	-1	0.5	**65**	145950.8	71682.1	-42250.9	-1	0
70	73941.6	1024379.0	-12701.4	-1	0.5	**70**	157100.1	71682.1	-42250.9	-1	0
75	84625.7	1024379.0	-12701.4	-1	0.5	**75**	168802.5	71682.1	-42250.9	-1	0
80	86052.2	1024379.0	-12701.4	-1	0.5	**80**	170144.6	71682.1	-42250.9	-1	0
85	81402.4	1024379.0	-12701.4	-1	0.5	**85**	166807.6	71682.1	-42250.9	-1	0
All	28751.8	1039461.0	-761.8	-1	1	**All**	139813.2	76254.3	-35634.4	-1	0
Teriparatide						**Teriparatide**					
50	-427352.3	4426244.0	2779850.0	-2	-0.5	**50**	571172.8	398696.8	-154031.5	-1	0
55	-472803.5	4426244.0	2779850.0	-2	-0.5	**55**	483853.2	398696.8	-154031.5	-1	0
60	-317091.8	4426244.0	2779850.0	-2	-0.5	**60**	619229.0	398696.8	-154031.5	-1	0
65	-325800.4	4426244.0	2779850.0	-2	-0.5	**65**	589516.7	398696.8	-154031.5	-1	0
70	-328248.4	4426244.0	2779850.0	-2	-0.5	**70**	616976.9	398696.8	-154031.5	-1	0
75	-286932.0	4426244.0	2779850.0	-2	-0.5	**75**	664552.7	398696.8	-154031.5	-1	0
80	-271457.8	4426244.0	2779850.0	-2	-0.5	**80**	679943.8	398696.8	-154031.5	-1	0
85	-298010.7	4426244.0	2779850.0	-2	-0.5	**85**	657700.0	398696.8	-154031.5	-1	0
All	-236285.8	5157181.0	2307670.0	-2	-0.5	**All**	535107.6	417461.7	-123200.2	-1	0

Chapter 7

MULTIDISCIPLINARY PORTUGUESE RECOMMENDATIONS ON DXA REQUEST AND INDICATION TO TREAT IN THE PREVENTION OF FRAGILITY FRACTURES

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Marques A, Rodrigues A, Romeu J, Ruano A, Barbosa A, Simões E, Águas F, Canhão H, Alves J, Lucas R, Branco J, Lains J, Mascarenhas M, Simões S, Tavares V, Lourenço, Ó, da Silva JAP. Multidisciplinary Portuguese recommendations on DXA request and indication to treat in the prevention of fragility fractures. Acta Reumat Port2 016(4);41:305-21.

ABSTRACT

Objective

To establish Portuguese recommendations regarding the indication to perform DXA and to initiate medication aimed at the prevention of fragility fractures.

Methods

A multidisciplinary panel, representing the full spectrum of medical specialties and patient associations devoted to osteoporosis, as well as national experts in this field and in health economics, was gathered to developed recommendations based on available evidence and expert consensus. Recently obtained data on the Portuguese epidemiologic, economic and quality-of-life aspects of fragility fractures were used to support decisions.

Results

Ten recommendations were developed covering the issues of whom to investigate with DXA and whom to treat with antifracture medications. Thresholds for assessment and intervention are based on the cost-effectiveness analysis of interventions at different thresholds of 10-year probability of osteoporotic fracture, calculated with the Portuguese version of FRAX® (FRAX®-Port), and taking into account Portuguese epidemiologic and economic data. Limitations of FRAX® are highlighted and guidance for appropriate adjustment is provided, when possible.

Conclusions

Cost-effectiveness thresholds for DXA examination and drug intervention aiming at fragility fracture prevention are now provided for the Portuguese population.

These are practical, based on national epidemiological and economic data, evidence-based and supported by a wide scope multidisciplinary panel of experts and scientific societies.

Implementation of these recommendations holds great promise in assuring the most effective use of health resources in the prevention of osteoporotic fractures in Portugal.

INTRODUCTION

Osteoporosis (OP) is a metabolic skeletal disease characterized by low bone mass and microarchitecture deterioration leading to increased bone fragility and susceptibility to fracture. In Portugal, the annual hip fragility fracture incidence is estimated to be between 154 to 572 per 100000 women and 77 to 232 per 100000 men, depending on age.[1] More than 10000 patients are admitted every year to the Portuguese National Health Service due to hip fragility fractures, justifying annual total health care expenditures of over 220 million euro. This corresponds to 1.4% of the total national health care expenditure in 2013, including private and public services, according to Portuguese Health Statistics.[2] The total expense with fragility fractures is much higher, as hip fractures only account for about 39.1% of the total number of fragility fractures observed in Portugal according to a recent study[3]

Altogether, osteoporotic fractures currently represent an enormous social and economic burden in Portugal, despite the fact that this country has one of the lowest incidences of fragility fractures in Western Europe.[1] The size of the problem will tend to increase relentlessly due to the increasing ageing of the population and other societal changes,[4] unless effective preventive measures are put in place.

This paper reports on the work of an Expert Committee convened to foster such measures, by providing physicians with practical and valid recommendations regarding the initiation of pharmacological treatment for osteoporosis and/or the request of DXA evaluation, in order to optimize the efficiency of interventions and minimize the costs and risks for individuals and society.

Since the last publication of recommendations for the diagnosis and treatment of osteoporosis in Portugal in 2007,[5] the FRAX® tool has been incorporated in the clinical guidelines for OP of several countries.[4 6-11] In fact, over half of the subjects who experience a fragility fracture do not have OP as defined by BMD.[12] FRAX® integrates a set of well-proven clinical risk factors for fracture, independent of BMD: age, gender, body mass index, prior fragility fracture, parental history of hip fracture, long-term use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking and alcohol intake, with or without BMD. It provides an estimate of the risk of major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and of hip fracture in the subsequent 10 years.[13 14] FRAX® provides valid predictions without BMD values,[15 16] although its accuracy increases when BMD is also considered.[17] This algorithm is applied upon the fracture epidemiology and death rates of each country, to provide locally optimized estimates of fracture probability. The FRAX® was derived from population-based cohort studies from

Europe, North America, Asia and Australia and has been validated in 62 countries and adopted by many as the key basis for decisions on whom to treat.

With this in mind, we have recently validated the FRAX model for the estimation of osteoporotic fracture probability in the protuguese population – FRAX®-Port[14] (http://www.shef.ac.uk/FRAX/tool.aspx?country=53). Through systematic literature review and meta-analysis [18] as well as consensus discussion we have decided that FRAX® is the most appropriate instrument to achieve similar purposes in Portugal. Among its advantages lies the possibility of using it even in the absence of BMD, allowing its output to decide if and when DXA is needed.

We have also performed a nation-wide careful evaluation of the costs of hip fractures and their impact upon quality of life and mortality.[19] The fracture risk probabilities above which the different interventions become cost-effective, in the actual Portuguese settings, were defined based on matured economic methodology, assisted by internationally renowned experts.[19]

These developments laid the optimal ground for a timely review of the Portuguese recommendations regarding the risk threshold for DXA investigation and pharmacological treatment of osteoporosis.

On these bases, we now recommend that decisions regarding the performance of dual X-ray absorptiometry (DXA) or the initiation of treatment are based on estimates of the actual risk of fracture and the economic implications of fractures and the different preventive strategies.

This report does not cover all possible management options and is not intended to override the individual physician's responsibility towards the patient or the personal choice of each patient. The authors wish to emphasize that formal guidance for every specific situation or co-morbidity cannot be provided due to lack of appropriate evidence. Judicious clinical judgment is required in such conditions.

This work, as well the series of supporting studies already published or under publication, have been funded by the Portuguese Government through the Direcção Geral da Saúde – DGS (Portuguese Health Directorate) following a proposal presented by Associação Nacional Contra a Osteoporose – APOROS (National Association Against Osteoporosis) and by an unrestricted grant from Amgen. None of the financial providers had any involvement in the design of the studies, interpretation of their results or the content of derived reports and recommendations.

A total of 10 recommendations were produced (Table 1).

Table 1. Summary of Recommendations on DXA request and indication to treat in the prevention of fragility fractures.

Recommendation	Votes	Average agreement % (Min.-Max.)
1 - The implementation of general, non-pharmacological, preventive measures for osteoporosis, such as diet, vitamin D supplementation, exercise, falls prevention and monitoring the use of any bone active drug should apply to all ages, whenever correctable risk factors are identified, irrespective of FRAX® and BMD.	Approved 17/17 votes	97 (75-100)
2 - Pharmacological treatment for osteoporosis should be recommended, unless contraindicated, in all subjects over the age of 50 who have previously experienced either A. ≥ 1 fragility fracture of the hip or ≥ 1 symptomatic vertebral fragility fracture or B. ≥ 2 fragility fractures, independently of the site of fracture or the absence of symptoms (e.g. two asymptomatic vertebral fractures).	Approved 17/17 votes	95.6 (70-100)
3 - All Portuguese women and men over the age 50 should have their 10-year risk of osteoporotic fracture estimated with the FRAX®-Port tool, with or without DXA.	Approved 17/17 votes	95.9 (80-100)
4 - The Committee recommends that for FRAX®-Port estimates, without DXA, between 7% and 11% for major osteoporotic fracture AND between 2.0% and 3% for hip fracture, BMD of the proximal femur, and, if possible and indicated, the spine should be assessed and the results of femoral neck T-score entered into FRAX®-Port. (see Figure 2). DXA may be justified in additional special conditions, as described in text.	Approved 16 votes 1 abstention	90.9 (60-100)
5.A - In men and women with a fracture risk estimate (without BMD) below 7% for major osteoporotic fractures AND 2% for hip fracture a decision not to treat with pharmacological agents may be warranted, without the need to perform DXA. Applicable general preventive measures should be applied.	Approved 16 votes 1 abstention	95.0 (50-100)
5.B - In such cases, FRAX®-Port estimates should be repeated with a frequency that depends on how close the previous estimate is to lower limit of indication to DXA and also on the occurrence of significant changes in clinical risk factors. (see Figure 2A)	Approved 16 votes 1 abstention	93.8 (60-100)
6 - In men and women with a fracture risk estimate, without DXA, above, 11% for major osteoporotic fracture OR 3% for hip fracture, pharmacological treatment with generic alendronate is cost-effective and should be advised (unless contra-indicated), without the need to perform DXA. (see Figure 2A)	Approved 16 votes 1 abstention	95.3 (80-100)
7 - In men and women with a FRAX®-Port 10-year risk-estimate, including DXA, at or above 9% for major osteoporotic or 2.5% for hip fractures pharmacological treatment for osteoporosis with generic alendronate is cost-effective and should be advised (unless contra-indicated). (See Table 1 and Figure 2B).	Approved 17/17 votes	93.2 (60-100)
8 - The decision to start anti-osteoporotic treatment with agents other than generic alendronate should be informed by their respective cost-effectiveness thresholds (see Table 4)	Approved 16 votes 1 Abstention	88.1 (0-100)
9.A - In men and women with a FRAX®-Port 10-year risk estimate, including DXA, below 9% for major osteoporotic AND below 2.5% for hip fractures, pharmacological agents are not cost-effective and a decision not to use them may be warranted. Applicable general preventive measures should be applied.	Approved 17/17 votes	96.5 (80-100)
9B - In such patients, DXA and FRAX®-Port assessments should be repeated every 2 years or whenever clinical risk factors change significantly (see Figure 2). DXA may not be needed in case the previous BMD values are reassuring.	Approved 16 votes 1 abstention	92.8 (75-100)
10 - While using FRAX®-Port for the sake of these recommendations, health professionals should be aware of several limitations of this tool and considerer judicious adjustments of the risk estimates provide by this tool in specific circumstances, described below.	Approved 17/17 votes	97.6 (70-100)

Please read the text for full understanding.

METHODS

Development of guidelines

A number of national experts on osteoporosis and all the relevant Portuguese scientific societies were invited and accepted to participate in the development of these recommendations: Rheumatology; Orthopaedics and Traumatology; Endocrinology, Diabetes and Metabolism; Gynaecology; Internal Medicine; Physical and Rehabilitation Medicine; Family Medicine, National Observatory for Rheumatic Diseases and Portuguese Society for Osteoporosis and Metabolic Bone Diseases. The only national patient organization active in the field of osteoporosis, Associação Portuguesa Contra a Osteoporose – APOROS, also participated in the Committee. Altogether, the Committee had 17 voting members, all of whom are co-authors of this report.

Relevant questions to be addressed by the recommendations were defined by consensus in a first round of e-mail consultations upon a draft prepared by the Principal Investigator (JAPS) and the research fellow (AM). A thorough literature review was performed in order to address each question (AM and JAPS) and made available to the committee members prior to the meeting. The electronic search was performed in PubMed MEDLINE (2006- January 15th 2015). The search strategies included the following medical descriptors: “Osteoporosis”, “Osteoporotic fractures”, “Risk Assessment”, “Algorithms,” “Recommendations”, “Guidelines”, ”treatment”, “Cost-effectiveness”, “Bone Mineral Density” and “DXA”. Original articles, reviews and guidelines regarding threshold for treatment initiation and DXA request were included in this review. References cited in published Systematic Reviews or in original articles were also checked.

Possible alternative answers to the elected questions, according to the collected evidence, were drafted by the principal investigator and submitted, together with the respective evidence, to the Expert Committee in a second round of emails. Committee members were asked to appraise the supportive evidence and alternative recommendations or to propose additional ones. All alternatives were circulated in a third round of e-mails, prior to the final face-to-face meeting.

This meeting was held on the 13th March 2015 to discuss the generated evidence, vote on the possible answers and thus generate a set of recommendations. The meeting was recorded for documentation and future clarification of doubts. The votes of individual representatives and degree of agreement regarding each recommendation were registered. Portuguese data on the cost-effectiveness of interventions according to different fracture risk thresholds were disclosed to the panel, for the first time, only after all the guiding principles, presented below, had been irrevocably established. They were only known to three of the

members, who performed the study (AM, OL, JAPS). This strategy was adopted to guarantee that the cost-effectiveness basis for the decision to intervene was based on the grounds of guiding principles and not contaminated by considerations of the percentage of the population eligible for intervention, its overall costs, or the (dis)similarity of our intervention thresholds *vis-a-vis* other published guidance.

A final round of e-mails was conducted to refine some recommendations.

Finally, this paper was drafted and circulated among the committee members until a final version was reached and submitted to the individual societies' and associations' approval and endorsement.

UNDERLYING CONCEPTUAL DEFINITIONS: GUIDING PRINCIPLES

As a preparatory phase for the definition of the recommendations, the Committee planned and developed a detailed discussion dedicated to the establishment of a number of guiding principles and concepts. These are presented below:

- **Guiding principle 1.**

Risk factors for osteoporosis, as those related with diet, exercise, sun exposure, medications, should be assessed by health professionals and patients throughout life, and corrected when appropriate.

This guiding principle was approved by all committee members (17/17 votes).

Many risk factors for osteoporosis influence bone health from the earliest phases and throughout life, even if the consequences of osteoporosis only become apparent later in life. This is the case, for example, of diet (calcium, protein), exercise, vitamin D status, and medications such as glucocorticoids. All these conditions have health implications far beyond the limits of bone health and should, therefore, be considered as a medical routine. The correction of these risk factors is an integral part of osteoporosis management, usually referred to as "General Measures".

- **Guiding principle 2.**

The decision to institute pharmacological treatment in osteoporosis should be based on the individual's 10-year risk of subsequent osteoporotic fracture as estimated by the FRAX®-Port tool.

This guiding principle was approved by all committee members (17/17 votes).

FRAX® is an algorithm developed under the auspices of the World Health Organization, which allows the estimation of the individual risk of osteoporotic fractures over the subsequent 10 years on the basis of 11 clinical risk factors (CRFs) that have been shown, through individual studies and meta-analyses, to influence the risk of fracture, independently of BMD. They are all easily available in clinical practice: age, weight, height, prior fragility fracture, parental history of hip fracture, current tobacco smoking, ≥ 3 months glucocorticoids use, rheumatoid arthritis, causes of secondary osteoporosis (type I diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease) and alcohol consumption. FRAX® can be used with or without BMD (Figure 1).

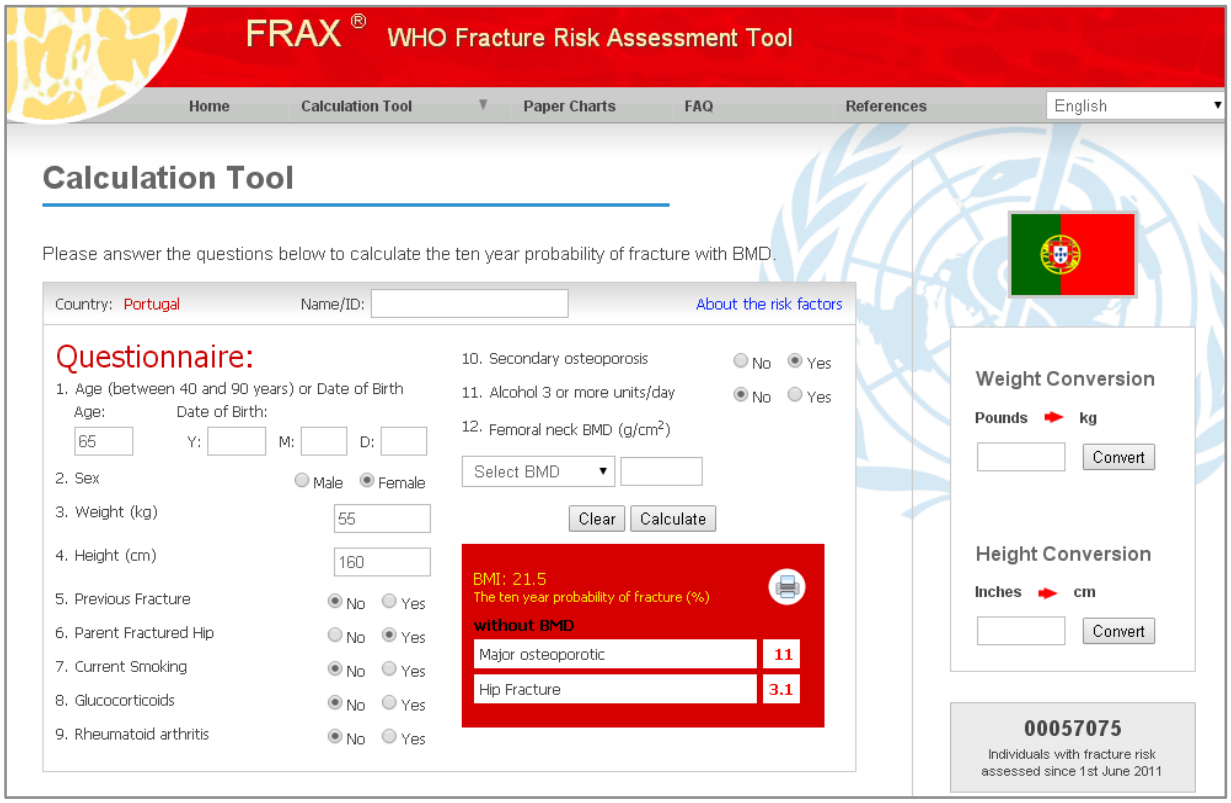

Figure 1. Screen page for input of data and risk estimation in the Portuguese version of the FRAX® tool (Portuguese model, version 3.9. - http://www.shef.ac.uk/FRAX/tool.aspx?country=53)

With permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK

When calculated using only CRFs, i.e., without considering BMD, FRAX® has been shown to have a better performance than BMD alone in predicting major fracture risk.[20] The development of this tool was based on excellent methodology[13] and its validity has been externally confirmed, up until now, by twenty-six studies performed in different countries and cohorts.[13 21-43] A total of 62 countries and/or ethnic models, are currently available and several others are being developed. [4]

A recent systematic literature review and meta-analysis performed by some of the Committee members[18] clearly demonstrated that FRAX is the most robust and accessible tool available to predict the risk of osteoporotic fractures. Its accuracy is well established and demonstrated by AUCs from ROC analysis for fracture prediction, that range from 0.71 to 0.79 in meta-analysis. This performance in only surpassed by the QFracture® tool,[18] but this instrument requires the consideration of 31 clinical risk factors and has only been validated for the UK and Ireland.

The FRAX®-Port tool is the Portuguese version of FRAX®, developed to incorporate the actual epidemiology of hip fractures and mortality in the general Portuguese population.[14] The methodology and results of this adaptation has been endorsed by the WHO cooperating center responsible for FRAX® and all Portuguese scientific societies and patients organization related to osteoporosis. It is readily available online.

- **Guiding principle 3.**

The presence of previous fragility fractures justifies the consideration of pharmacological treatment, irrespective of the risk-estimate by the FRAX®-Port tool.

This guiding principle was approved by 15 favorable votes, 1 against and 1 abstention.

Several studies support the conclusion that it is cost-effective to treat individuals with a prior hip or vertebral fragility fracture.[7 8 44] Vertebral fractures, for example, are a very strong risk factor for subsequent hip and vertebral fracture,[45 46] whereas forearm fractures predict future vertebral and hip fractures,[47]

The vote against was justified on the basis that previous fractures are already accounted for in FRAX®.

The time elapsed since the last previous fracture is also relevant: the risk of further fractures is greatest during the first 2–3 years but remains significantly elevated for up to 10–15 years (most notably for proximal femoral fractures, vertebral fractures, and humeral fractures). [48 49]

- **Guiding principle 4.**

Physicians should be aware of the limitations of FRAX® and of DXA, and make judicious informed adaptations of the fracture risk estimate when such limitations apply.

This guiding principle was approved by all committee members (17/17 votes).

- **Guiding principle 5.**

Portuguese intervention thresholds should be based on a similar FRAX® 10-year risk estimate for all ages. This principle should only be overruled if the health-economics evaluations demonstrated that the intervention threshold for any given age and gender group differs more than 50% from the value recommended on the basis of the overall population.

This guiding principle was approved by 10 favorable votes, 4 against and 3 abstentions.

This was one of the most controversial points in the consensus meeting. The final recommendation is similar to the guidelines adopted by the National Osteoporosis Foundation – USA [11] and Canada.[10] In both these cases, the threshold for intervention was defined as the level of risk above which the cost per QALY gained was within the national acceptable limits. In both these guidelines, a similar value of estimated risk of fracture was adopted as the threshold for intervention for all ages and both genders, despite there being small age- and gender-related differences in the levels of risk that defined cost-effectiveness.

The recommendations issued by the United Kingdom's Royal College of Physicians,[44] the Swiss association Against Osteoporosis[8] and the French National Authority for Health[6] adopted a different conceptual drive: Treatment is recommended for all people whose 10-year FRAX® estimated risk is equal or superior to that of a female patient of similar age, who has already suffered a fragility fracture. This concept is based on the fact that treatment in people with a previous fragility fracture has been shown to be cost-effective. Given that the risk of fracture increases with age, all other things being equal, this approach determines that the intervention threshold increases substantially with age. As an example, according to the UK guidance referred above, treatment will be recommended for a 50 year old whose 10-year risk of fracture is 7.5% but not for a 70 year-old whose 10-year estimated risk is 24%. The majority of our committee refused this philosophical approach. This was based mainly on the argument that the gain of one QALY should be considered of the same value for all ages. It was emphasized that age, as well as mortality are already considered in FRAX® and thus influence the fracture risk estimate. Overall, the majority of the committee decided to stand by the concept that, for the sake of equity, similar gains in health, as measured by QALYs, should justify similar financial efforts by society, irrespective of age.

- **Guiding principle 6.**

The Portuguese intervention thresholds should be based on cost-effectiveness data.

This guiding principle was approved by all committee members (17/17 votes).

By doing this, the Committee decided to accept that the threshold for intervention, at a

population level, should be informed by economic considerations, rather than on a "political" perspective of a level of risk that would justify intervention, irrespective of its costs and societal willingness to pay. The committee thus acknowledges that the cost of intervention and the societal willingness to pay needs to be taken into account in decisions to treat or not to treat.

This principle implies that decisions to treat should have a similar foundation in all realms of medicine in our country – the impact of interventions in terms of QALYs gained should be calculated, the cost per QALY gained (or Incremental Cost-Effectiveness Ratio – ICER) determined and, naturally, a similar willingness to pay for a QALY should be applied, whatever the disease and intervention under consideration.

- **Guiding principle 7**

The intervention thresholds should be based on data reflecting the Portuguese reality on fractures, mortality, costs and treatment efficacy.

This guiding principle was approved by all committee members (17/17 votes).

Recommendations on the level of fracture risk above which pharmacological intervention become cost-effective are inextricably dependent on dimensions that vary enormously at a national level, such as: epidemiology of fractures, general mortality, mortality associated with fractures, medical interventions used in fracture cases, costs of caring for fractures, costs of preventive interventions, health policies, cost per QALY gained (ICER), economic status of the country and willingness to pay. This imposes the need to consider national data when making such decisions, and requires that intervention-threshold recommendations for Portugal had to wait until such data became available.

- **Guiding principle 8.**

The threshold for pharmacological treatment of osteoporosis shall be established at 10-year risk estimates that correspond to a Willingness to Pay per QALY gained of €32,000.

The cheapest of all pharmacological interventions should be taken as the basis to decide on the actual intervention threshold for the Portuguese population.

This guiding principle was approved by 16 favorable votes and 1 abstention.

Cost-effectiveness of a given intervention can only be established by comparing its impact to a set value of willingness to pay for a QALY gained [50]. There is no established Portuguese national policy establishing Willingness to Pay for QALYs. So, the panel decided to endorse the recommendations issued by WHO, that this should be set at 2 fold the National Gross

Product per capita[51] – 32.000€ is a rounding up of 2 X 16.400€, the Portuguese GDP for year 2014.[52]

The choice for the cheapest intervention as a reference is based on the fact that the costs as well as the effectiveness of each of the available alternatives are taken into account while establishing the respective Cost per QALY (ICER).

All the above decisions were made before the actual cost-effectiveness studies for Portugal were presented to the Committee.

- **Guiding principle 9.**

DXA should be performed when it has a reasonable probability of changing the decision to treat/not to treat that can be taken on the basis of the FRAX®-Port risk estimation made without DXA.

This guiding principle was approved by 16 favorable votes and 1 abstention.

Adding DXA to CRFs in FRAX® results, according to our meta-analysis, in the improvement of the AUC from 0.74 to 0.79.[18] DXA may also assist the clinician in gauging the probability of secondary osteoporosis, in quantifying response to therapy and motivating the patient to treatment. The Committee considered that performing one DXA examination, at the time of deciding whether to treat, represents a relatively minor cost in view of the overall burden of the disease, which is compensated by the benefits than can be derived from that exam. This perspective led to a less stringent recommendation on when to perform DXA.

Based on this guiding principle the following concepts were defined for the purposes of these recommendations:

- **Intervention threshold** A FRAX®-Port 10-year risk-estimate value, with BMD, above which pharmacological treatment is warranted.
- **Range of fracture risk indicating the need for DXA:** A range of FRAX®-Port 10-year risk-estimate, without BMD, within which DXA is justified, because it holds a reasonable probability of changing the decision to treat or not-to-treat.

Ideally, the lower and upper threshold for DXA evaluation would be based on real life Portuguese data establishing the probability of BMD inducing a change in the decision to treat/not to treat, around the intervention threshold. In the absence of such data, and taking into account the issues described above, the Committee consensually decided to establish these values at 2% and 0.5% above and below the intervention threshold for major osteoporotic and for hip fractures respectively.

COST-EFFECTIVENESS ANALYSIS

Once the above Guiding Principles were adopted, the Portuguese cost-effectiveness analysis with generic alendronate (the less expensive intervention) versus no treatment was presented to the Committee (see Table 2).

A detailed study in a representative sample of Portuguese patients with hip fractures was performed to establish the impact of osteoporotic fractures in terms of resource consumption (direct and indirect costs), mortality and quality of life. A societal perspective was adopted, i.e. all costs were considered irrespective of the payer being the patient or the security system. [19]

These data were incorporated in a previously validated Markov economic model[53] which synthetized relevant available data, such as the incidence of fractures and their age distribution, the general population mortality, the cost, effectiveness and risk of adverse events of the different medications, need for co-medications and control procedures and drop-out rates. This model allows the estimation of Incremental Cost-Effectiveness Ratio – ICER, for each intervention, a concept that can be understood as the cost paid for each QALY gained, in comparison to no treatment. The results were used to establish the levels of estimated risk of fracture at which each given intervention becomes cost effective, i.e. results in costs per QALY within the established willingness to pay.

Based on the published results,[54] the Committee decided to adopt the FRAX®-Port risk estimates of 9% for major osteoporotic fractures and 2,5% for hip fractures as the intervention thresholds for generic alendronate, in Portugal – Table 2. The values for assessment threshold were established as 2% and 0.5% above and below the threshold of intervention for major osteoporotic or hip fractures, respectively.

Table 2. Cost-effective intervention thresholds expressed as the 10-year probability of a major /hip fracture (%) at which intervention with generic alendronate becomes cost-effective in comparison to no treatment, adopting a willingness to pay of €32,000.00/QALY.

Age	10-year probability of a major fracture (%)	10-year probability of a hip fracture (%)
50	8.6	2.6
55	8.7	2.4
60	10.4	3
65	9.2	2.3
70	8.6	2.3
75	8.1	2.1
80	7.1	1.7
85	5.9	1.3
All	8.8	2.5

The intervention threshold for "All ages" is not the arithmetic mean of the individual age-groups values but the result of QALY calculations including the overall population.
Adapted from Marques A, Lourenco O, Ortsater G, et al. Cost-effectiveness of intervention thresholds for the treatment of osteoporosis based on FRAX in Portugal. Calcified tissue international 2016;99(2):131-41.[54]

RECOMMENDATIONS

- **Recommendation 1.**

The implementation of general, non-pharmacological, preventive measures for osteoporosis, such as diet, vitamin D supplementation, exercise, falls prevention and monitoring the use of any bone active drug should apply to all ages, whenever correctable risk factors are identified, irrespective of FRAX® and BMD.

This recommendation was approved by all committee members (17/17 votes) and an average agreement of 97 % (75-100).

- **Recommendation 2.**

Pharmacological treatment for osteoporosis should be recommended, unless contraindicated, in all subjects over the age of 50 who have previously experienced either

A. ≥ 1 fragility fracture of the hip or ≥ 1 symptomatic vertebral fragility fracture or

B. ≥ 2 fragility fractures, independently of the site of fracture or the absence of symptoms (e.g. two asymptomatic vertebral fractures).

This recommendation was approved by all committee members (17/17 votes) and an average agreement of 95.6 % (70-100).

Specifications to Recommendation 2.

- For this purpose, a fragility fracture is defined as a fracture occurring spontaneously or following minor trauma, i.e. similar or inferior to that of a fall from body height, after exclusion of pathological local causes of fracture such as neoplasia.
- This recommendation implies that the presence of such fractures overrides the FRAX®-Port, i.e. treatment should be considered in these patients irrespective of FRAX®-Port risk-estimate or DXA measurements. This does not imply that FRAX® or DXA should not be performed, as they may provide useful information to guide further investigation and choice of therapeutic interventions.

Recommending treatment for people who have already endured a fragility fracture, irrespective of FRAX® is common to all of the abovementioned recommendations: NOF-USA[7] Canada,[10] France[6] and Switzerland.[8] This concept is inherent to the NOGG/UK recommendations.[44] The exact definition varies between documents. No evidence was found

to propose the inclusion of ≥2 fragility fractures (other than hip or clinical vertebral) for treatment without further assessment. This was a consensus recommendation, based on the authors' opinion and experience.

- **Recommendation 3.**

All Portuguese women and men over the age 50 should have their 10-year risk of osteoporotic fracture estimated with the FRAX®-Port tool, with or without DXA.

This recommendation was approved by all committee members (17/17 votes) and an agreement of 95.9 % (80-100).

Specifications to recommendation 3.

- The decision to perform DXA should, ideally, be based on this initial FRAX®Port without BMD, as described below. However, if a recent BMD is already available, its value should be entered in the FRAX®-Port calculation. The decision process for treatment should, in such case, be based on Recommendations 7, 8 and 9. DXA values can be acceptable for this purpose for up two years, unless significant events for bone metabolism take place meanwhile.
- Physicians are strongly recommended to strictly adhere to the definitions of clinical risk factors as described in the FRAX® website

- **Recommendation 4.**

The Committee recommends that for FRAX®-Port estimates, without DXA, between 7% and 11% for major osteoporotic fracture AND between 2% and 3% for hip fracture, BMD of the proximal femur, and, if possible and indicated, the spine should be assessed and the results of femoral neck T-score entered into FRAX®-Port. (see Figure 2).

DXA may be justified in additional special conditions, as described below.

This recommendation was approved by 16 favorable votes and 1 abstention with an average agreement of 90.9% (60-100).

Specifications to recommendation 4

- For the purposes of this recommendation, BMD should be assessed by dual x-ray absorptiometry (DXA).

- The spine and proximal femur, are the sites recommended for DXA evaluation [55]. Spine DXA is prone to overestimate BMD in the presence of osteoarthritis, vertebral fractures and other calcifying changes overlaying the sites of interest.
- The T score value for the femoral neck should be used for FRAX®-Port
- In the context of decision to/not-to treat, DXA results must be considered in the context of FRAX®-Port and not in isolation. This principle implies that the diagnosis of osteoporosis or osteopenia based on densitometry does not, *per se*, warrant the initiation of pharmacological treatment for osteoporosis.
- The use of DXA for monitoring therapy is controversial, it is rarely justifiable at intervals of less than 2-3 years and may be dispensable altogether if the adherence to effective therapy is guaranteed (for more info on the appropriate use and interpretation of DXA see references [17 56 57]).
- The committee considers that performing DXA may occasionally be justified outside these FRAX boundaries or irrespective of them, including in the conditions described in Table 3.

Table 3. Conditions/diseases and treatments with impact upon BMD, as established by systematic literature reviews and/or meta-analysis

Patients with the following conditions/diseases	Patients starting or under the following medications
Fragility fracture ≤ 50 [58]	Androgen deprivation therapy [59-61]
Prolonged immobilization and paralysis[62 63]	Glucocorticoids [64]
Falls history [4 5 7 10 17]	Anticonvulsants [65]
Anorexia nervosa [66 67]	Gonadotropin-releasing hormone analogues (GnRH)[68-70]
Calcium and vitamin D deficiency [4 7 71 72]	Aromatase inhibitors [73-77]
Intestinal absorption [7 78]	Antiretroviral therapy [72 79]
Rheumatoid arthritis [80]	
Hyperparathyroidism [81 82]	

Other conditions, with less well-established relationship with osteoporosis, may also justify the performance of DXA as part of the diagnostic work-up. These include Cystic fibrosis; Ehlers-Danlos; Gaucher's disease; Glycogen storage diseases; Hemochromatosis; Homocystinuria; Hypophosphatasia; Marfan syndrome; Menkes steely hair syndrome; Porphyria; Riley-Day syndrome; Athletic amenorrhea; Hyperprolactinemia; Panhypopituitarism; Turner's and Klinefelter's syndromes; Cushing's syndrome; Thyrotoxicosis; Gastric bypass; Gastrointestinal surgery; Pancreatic disease; Primary biliary cirrhosis; Hemophilia; Leukemia; Lymphomas; Monoclonal gammopathies; Multiple myeloma; Sickle cell disease; Systemic mastocytosis; Thalassemia; Ankylosing spondylitis; Systemic lupus erythematosus; Amyloidosis; Chronic metabolic acidosis; Chronic obstructive

lung disease; Congestive heart failure; Depression; End-stage renal disease; Hypercalciuria; Idiopathic scoliosis; Post-transplant bone disease; Sarcoidosis; type I diabetes mellitus.

Some medications, with less well-established relationship with osteoporosis, may also justify the performance of DXA in special cases. These include: Aluminum (in antacids); Anticoagulants (heparin); Barbiturates; Cancer chemotherapeutic drugs; Depo-medroxyprogesterone; Lithium; Cyclosporine A and tacrolimus; Methotrexate; Parental nutrition; Proton pump inhibitors; Selective serotonin reuptake inhibitors; Tamoxifen®; Thiazolidinediones (such as Actos®; Thyroid hormones (in excess)).

- **Recommendation 5.**

5A. In men and women with a fracture risk estimate (without BMD) below 7% for major osteoporotic fractures AND 2% for hip fracture a decision not to treat with pharmacological agents may be warranted, without the need to perform DXA. Applicable general preventive measures should be applied.

This recommendation was approved by 16 favorable votes and 1 abstention with an average agreement of 95 % (50-100).

5B. In such cases, FRAX®-Port estimates should be repeated with a frequency that depends on how close the previous estimate is to lower limit of indication to DXA and also on the occurrence of significant changes in clinical risk factors. (see figure 2A)

This recommendation was approved by 16 favorable votes and 1 abstention with an average agreement of 93.8 % (60-100).

Regarding recommendation 5B the Committee presumes that FRAX®-Port reassessments will, on average, in such cases, be justified every 5 years from age 50 to 70 and every two to three years thereafter, in the absence of relevant intercurrences.

- **Recommendation 6.**

In men and women with a fracture risk estimate, without DXA, above, 11% for major osteoporotic fracture OR 3% for hip fracture, pharmacological treatment with generic alendronate is cost-effective and should be advised (unless contra-indicated), without the need to perform DXA. (see figure 2A)

This recommendation was approved by 16 favorable votes and 1 abstention and an average agreement of 95.3 % (80-100).

- **Recommendation 7.**

In men and women with a FRAX®-Port 10-year risk-estimate, including DXA, at or

above 9% for major osteoporotic or 2.5% for hip fractures pharmacological treatment for osteoporosis with generic alendronate is cost-effective and should be advised (unless contra-indicated). (See Table 2 and Figure 2B).

This recommendation was approved by all committee members (17/17 votes) with an average agreement of 93.2 % (60-100).

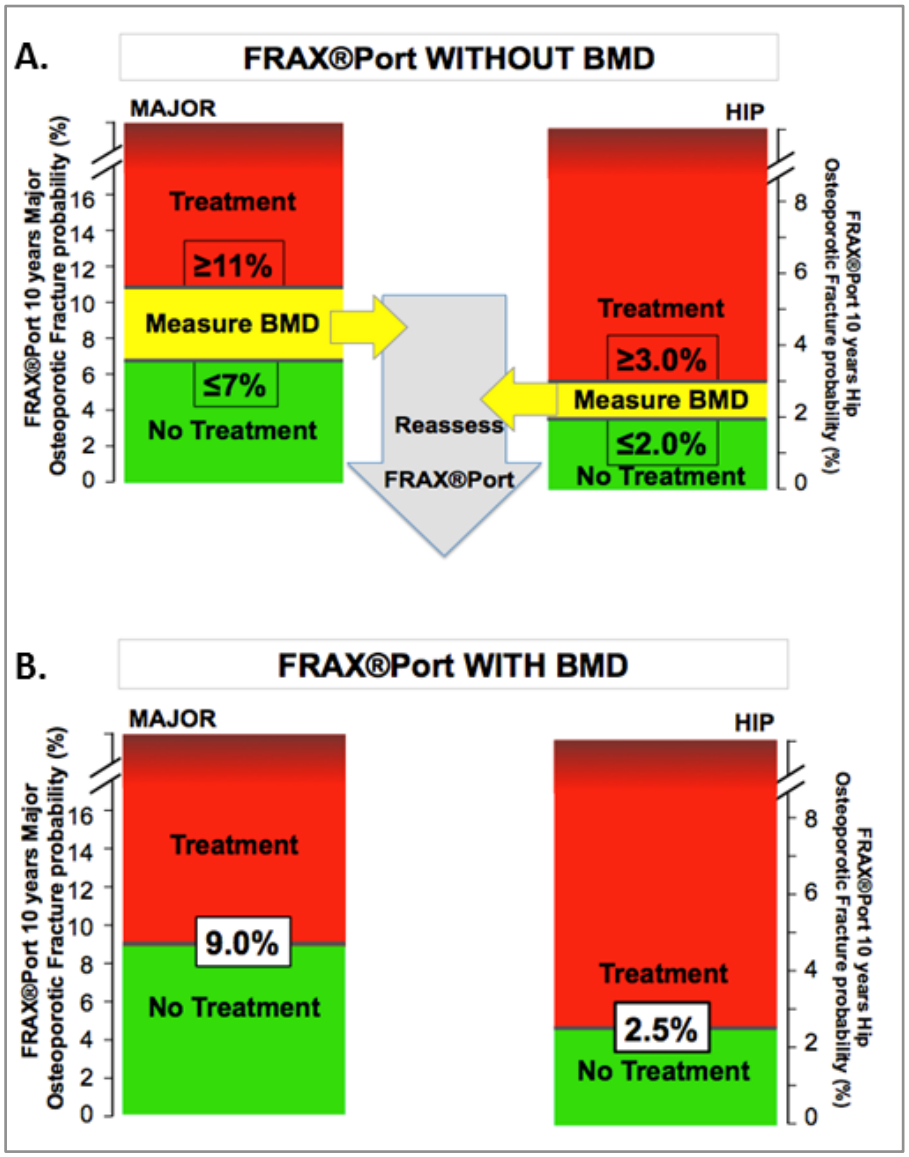

Figure 2. Use of FRAX®-Port 10-year estimated risk of Major Osteoporotic and Hip Fractures to decide on request of DXA and on initiation of pharmacologic treatment for osteoporosis. **A.** Estimates without BMD. **B.** Estimates with BMD.

- **Recommendation 8.**

The decision to start anti-osteoporotic treatment with agents other than generic alendronate should be informed by their respective cost-effectiveness thresholds (see Table 4)

This recommendation was approved by 16 favorable votes and 1 against with an average agreement of 88.1 % (0-100).

Specifications to recommendation 8.

- This recommendation does not preclude the decision to prescribe these medications at lower risk-estimates, based on clinical grounds, such as formal-contraindication to less expensive alternatives, or conditions making the selected choice especially appropriate. The individual physician may also decide to adopt a different willingness to pay.

This specification was approved by 16 favorable votes and 1 against and an average agreement of 99.3% (90-100).

The cost per QALY associated with different medications is affected by their cost and effectiveness in different clinical settings. Table 4 presents the risk-estimate levels at which treatment with zoledronic acid, denosumab and teriparatide become cost-effective in comparison to no-treatment and may, thus, be recommended on cost-effectiveness grounds, as described by Marques et al.[54]

The authors want to highlight that no national data is available on cost-effectiveness thresholds for other drugs. The only alternative is to extrapolate based on indicators of effectiveness, persistence and cost of those alternative drugs compared to the studied options.

Table 4. Cost-effectiveness thresholds for several medications, based on the FRAX®-Port 10-year osteoporotic fracture risk estimate, for different medications, based on a Willingness to Pay of 32.000€/QALY and current cost of medication.

		Without DXA		**With DXA**	
	Cost basis/year (€)	**Major %**	**Hip %**	**Major %**	**Hip %**
Generic alendronate	99	11	3	9	2.5
Zoledronic acid	347	22	12	20	10
Denosumab	552	37	25	35	23
Teriparatide	4234	80	65	78	63

Adapted from Marques. A LO, Ortsäter. G, Borgström. F, JAP da Silva. Cost-effective osteoporosis treatment intervention thresholds based on FRAX® in Portugal. Calcified tissue international 2016;99(2):131-41.[54]

- **Recommendation 9.**

9.A. In men and women with a FRAX®-Port 10-year risk estimate, including DXA, below 9% for major osteoporotic AND below 2.5% for hip fractures, pharmacological

agents are not cost-effective and a decision not to use them may be warranted. Applicable general preventive measures should be applied.
This recommendation was approved by all committee members (17/17 votes) and an average agreement of 96.5 % (80-100).

9B. In such patients, DXA and FRAX®-Port assessments should be repeated every 2 years or whenever clinical risk factors change significantly (see Figure 2). **DXA may not be needed in case the previous BMD values are reassuring.**
This recommendation was approved by 16 favorable votes 1 abstention and an agreement of 92.8% (75-100).

- **Recommendation 10.**

While using FRAX®-Port for the sake of these recommendations, health professionals should be aware of several limitations of this tool and considerer judicious adjustments of the risk estimates provide by this tool in specific circumstances, described below.
This recommendation was approved by all committee members (17/17 votes) with an average agreement of 97.6 % (70-100).

Specifications of recommendation 10

- The limitations of FRAX®-Port are the same as those of FRAX®. Some of these may be resolved in future revisions of the tool;
- FRAX® does not take into account the number of prior fragility fractures [17], but this limitation is overcome by the Committees decision to recommend previous fragility fracture as an independent criterion to start treatment.
- FRAX® has not been validated to be used in patients under osteoporotic treatment or for monitoring the effects of treatment [17].

These specification was approved by 16 favorable votes, 1 abstention and an average agreement of 100%.

- Falls are an important clinical risk factor for fractures and are not included in the FRAX® tool.[83] No formal recommendation can be made for this purpose, due to lack of appropriate scientific evidence. The best reference values that we can be provided are based on calculations performed with the QFracture®2013, [84] [85]a validated and accurate fracture risk estimation tool, which considers falls. In this context, the

presence of a “history of falls”, multiplies by a factor of around 1.5, the 10-year fracture risk estimate made in its absence.

This specification was approved by all committee members (17/17 votes) and an average agreement of 92.1 % (0-100).

- The FRAX tool does not take into account the corticosteroid dose above 5mg Prednisolone equivalent for three months. The Committee recommends that the 10-year probabilities of a hip fracture or a major osteoporotic fracture be adjusted according to the dose of glucocorticoids as described in Table 5. No adjustments regarding duration of treatment can be proposed, due to lack of appropriate evidence.

This specific recommendation was approved by 16 favorable votes, 1 abstention and an average agreement of 87.5% (50-100).

Table 5. Recommended adjustment of 10-year probabilities for major osteoporotic fracture or hip fracture for all ages according to daily dose of glucocorticoids.

	Adjustment factor for ten year-probability estimates (for all ages)	
Prednisolone equivalent (mg/day)	**Major osteoporotic fracture**	**Hip fracture**
<2.5	0.8	0.65
2.5–7.5	No adjustment	No adjustment
≥7.5	1.15	1.20

Adapted from Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013;24(1):23-57.[4 86] and from Kanis JA, Johansson H, Oden A, et al. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int. 2011;22(3):809-16.[4 86]

Multiply the FRAX®-Port fracture risk estimate by the provided adjustment factor.

- FRAX® algorithm uses T-score for femoral neck BMD and does not take into account the lumbar spine BMD. However, when there is a large discordance (> 1SD) in the T-score of femoral neck and lumbar spine, it is proposed that the clinician may increase/decrease FRAX® estimate for major osteoporotic fractures by 10% for each rounded T-score difference between the lumbar spine and femoral neck.[4 87]

  For example if T-score femoral neck = -1.5 and T-score lumbar spine = -2.8, the FRAX® estimate for major osteoporotic fractures should be increased by 10% percent (for example from 7% to 7.7%). If the values were -1.5 and -1.9 respectively, no changes should be made (difference <0.5 T). If femoral neck T score = -2.3 and lumbar spine T score = -3.9, the difference (1.6) is rounded to 2 T score and the major osteoporotic fractures risk estimate should be increased by 20% (for example from 8% to 9.6%, justifying medication according to the present recommendations).

  As in all other circumstances, it is important to guarantee the quality and validity of lumbar spine DXA.

This specification was approved by all committee members (17/17 votes) and an agreement of 91.5% (75-100).

In Figure 3 we present a simplified integrated flow chart of decisions on treatment and DXA assessment according to the current recommendations. Take into account that the intervention thresholds are based on calculations for generic alendronate. Please refer to recommendation 8 to adapt for other medications.

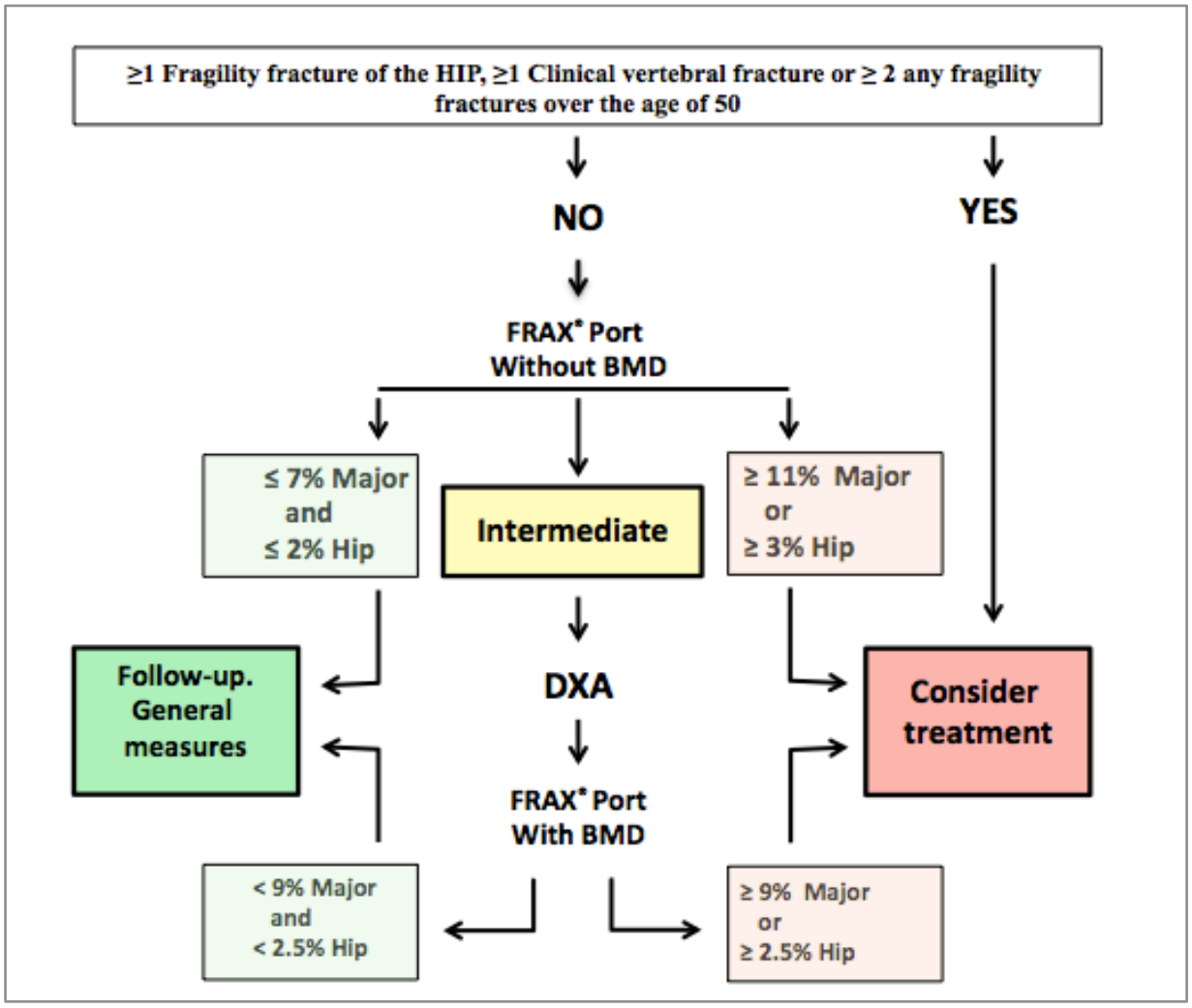

Figure 3. Integrated approach of osteoporosis intervention thresholds and DXA request for Portuguese patients according to the current recommendations.

Intervention thresholds described in this figure are appropriate for generic alendronate. Consider recommendation 8 (Table 6) for other agents.
BMD, bone mineral density. DXA, Dual-energy X-ray absorptiometry * Follow up- Repeat assessments as suggested in recommendations 5B and 9B.

DISCUSSION AND FINAL REMARKS

Ten recommendations regarding who to treat for osteoporosis and who to examine with DXA in daily clinical practice have been developed for Portuguese patients, based on

consensualized guiding principles and updated epidemiologic and economic evaluations in the Portuguese setting (Table 1). The recommendations are practical, evidence-based and supported by a panel of experts and representatives of all Portuguese scientific societies and patients' associations with an interest in Osteoporosis.

Evidence was used as the basis for recommendations as much as possible and this was supplemented by collegial decisions of the experts when decisive evidence was lacking. Considerable effort was put in to trying to keep the recommendations as simple, but also comprehensive, i.e. capable of responding to most of the practicing clinicians needs.

These recommendations provide a much more robust and rationale basis for treatment decisions than considering solely the bone mineral density (BMD) or asking clinicians to base decisions on a subjective weighting of clinical risk factors. FRAX® allows the integration of a large number of clinical risk factors for fractures, whose relevance has been proven by evidence and whose impact has been estimated by meta-analysis. Moreover, the Portuguese version of FRAX incorporates the actual epidemiology of fragility fractures and mortality in the target population. The consideration of cost-effectiveness analyses of interventions in our actual epidemiologic and economic context, responds to the responsibility of making judicious use of the limited resources available for health care. These calculations were performed using state-of-the-art economic models and prestigious economic counseling. The adopted willingness to pay follows international recommendations.

A certain degree of arbitrariness was used in establishing the same cost-effective intervention threshold for all ages, despite there being considerable variability between the age groups. The same applies to the amount adopted as WTP: some practitioners may have a different view and the WTP may change according to GDP and national health policies. Expert users may wish to produce a more precise definition of cost-effective threshold for specific individual cases, taking into account the patient's age, the medication being considered or a WTP of their own choice. This can be achieved through the use of a dedicated tool made available by Marques et al.[54] at https://dl.dropboxusercontent.com/u/4287154/OsteoporoseThrCalc/ThreshComputationPortugalFINAL.xlsm.

These recommendations represent an important paradigm shift, which was made possible by the development of FRAX®, its Portuguese adaptation and the economic evaluations described above. We believe that the potential of this change towards supporting a more efficient use of human and financial resources in the combat to the ever-growing epidemics of osteoporotic fractures is truly enormous. However, it all depends on the use that health professionals, both individually and as a community, make of these new tools. It is expected that the endorsement of these recommendations by all the experts and societies represented will increase their dissemination and implementation into national clinical practice, thus

expanding their potential to foster progress on the current standard of osteoporosis management in our country.

We will be greatly indebted to all health professionals who may be willing to share their views and experiences on using these recommendations and offer suggestions on how to improve their reach on behalf of public health (reuma@huc.min-saude.pt).

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Chapter 8

FRAX®-PPP (FRAX®-PORT PATIENT PROJECT): A POPULATION-BASED OSTEOPOROSIS INTERVENTION PROGRAM USING FRAX®

Preface

This chapter presents a research and intervention project, which has been designed by the authors. Partial financial support has been acquired and the internet tool is in the final stages of preparation. The program will be launched over the next few months.

The project is described below in the exact terms used to present it to funding bodies (Nursing School of Coimbra, Faculty of Medicine, University of Coimbra, WHO, Pharmaceutical companies).

This project can only be developed due to all previous work performed by the authors.

Introduction

Osteoporotic fractures represent a major public health problem, with an enormous social and economic impact particularly in countries with an aged population, such as Portugal.[1 2] Scientific estimates suggest that, in the year 2000, around 9.0 million osteoporotic fractures occurred worldwide of which 1.6 million were at the hip, 1.7 million at the forearm and 1.4 million were clinical vertebral fractures.[3] We have recently found that a total of 51701 osteoporotic fractures of the hip alone occurred in Portugal (population ~10 million) from 2006 to 2010.[4]

According to the available data, 10 to 20% of these patients can be expected to die within one year and 50% become unable to walk without support and therefore institutionalized or dependent on others for simple personal care.[5-7] Unless effective measures are put in place this burden will more than double in the next 40 years.[8] However, a substantial proportion of these osteoporotic fractures are preventable, with the adoption of healthy behaviours, such as a proper diet, including calcium and vitamin D supplements, if needed, regular exercise and avoiding excess of alcohol, tobacco and other substances that interfere with bone metabolism and health.[9] Lack of information or ability to understand and deal with the information available, keep many people oblivious of simple measures they could adopt to prevent osteoporosis and fractures associated with it.[10] By improving people's access to health information and their capacity to use it effectively, health literacy is critical to empowerment and to the success of public health programs. [8 11]

The FRAX® tool has been developed by the World Health Organization (WHO) to estimate the fracture risk of individual patients.[12] This algorithm takes into account the national epidemiology of fractures and considers the clinical risk factors observed in each individual and well as well as bone mineral density (BMD) at the femoral neck (if available), to estimate the probability of an osteoporotic fracture occurring over the following ten years.[13] We have recently established the FRAX® tool for use in the Portuguese population (FRAX®-Port), in cooperation with WHO, allowing the computation of fracture probabilities calibrated to the epidemiology of Portugal.[4]

The FRAX® tool is a major advance in the management of osteoporosis in both postmenopausal women and men aged above 50 years. Risk estimates derived from FRAX® can and should constitute the basis for the selection of preventive measures, which should be adapted, in nature and urgency, to the level of risk identified.[13-15]

It is now widely recognized that individuals with limited health literacy have poorer health status, are less likely to use preventative care and are more likely to be hospitalized and have bad disease outcomes.[16 17] Poor health literacy also contributes to increase inpatient spending, and after controlling for relevant covariates, lower health literacy scores were associated with higher mortality rates and health costs.[18-20]

As consequence there is a move towards "patient-centred" health care as part of an overall effort to improve the quality of health care provision and contain costs.[21] Patients are invited to take an active role in health related decisions.[22] Health care providers are required to utilize effective health communication skills and methods, including techniques adapted to adult education such as "teach-back".[i]

As so patient centered care programs should integrate new technologies for health (eHealth), that can be utilized to increase patient engagement in the screening of several diseases, which resulted in a higher level of satisfaction, increased understanding of their care, improved engagement, and better compliance to behaviors prescribed by their health professional.[23-27]

Several studies have demonstrate that for people with chronic diseases, access to electronic health information (eHealth) is an important tool to help those individuals manage their condition and make informed choices about their health.[28]

The easy access, simplicity and interactivity of the FRAX® tool makes it the ideal to be used as a tool to increase public awareness about bone health and foster timely and effective intervention, through active involvement of the population in osteoporosis screening. Successful interventions of this nature have already been documented in cardiovascular disease, diabetes and in mental health.[16 29] We believe that the same can be achieved, with great benefit, in osteoporosis.[30]

General concept

Through this work we aim to foster the general public involvement in a campaign to curtail the ever-growing burden of osteoporosis. This will be served by an awareness campaign and a web platform that allows lay members of the general population to calculate their subsequent 10 years' probability of osteoporotic fracture (using FRAX® Port) and to act upon

[i] To learn more about "teach-back" techniques visit http://www.teachbacktraining.org/

this information. Opportunities for action include changes in lifestyle or a visit to their physician/health professional, as appropriate. The platform will also provide information regarding osteoporosis causes, consequences and prevention strategies.

Objectives

- To promote awareness of osteoporosis among the general public;
- To foster preventive healthy behaviours relevant to osteoporosis;
- To promote the self-screening of osteoporosis by the general population;
- To promote early adequate management of patients at risk of fracture;
- To increase adherence to pharmacologic and non-pharmacologic treatment of osteoporosis;
- To increase the awareness of physicians/health professionals regarding osteoporosis and the use of FRAX®;
- To increase the capacity of individuals to obtain, process, and understand basic health information and services needed to make appropriate health decisions;
- Ultimately: to reduce the incidence of osteoporotic fractures in Portugal.

Methodology

The project will be based on a dedicated web platform. This will be organized in seven different areas:

1. Home page
2. What is osteoporosis? Why should I care?
3. My probability of suffering a fracture over the next ten years.
4. What should I do?

a. Should I seek the help from a health professional?

b. What else can I do to prevent osteoporosis and have healthy bones?

5. Where can I find more information?
6. Feedback on the web platform. Report of actions taken as a result of its use.
7. Discussion forum for patients, supported by health professionals

Plain language will be used throughout the website after and all written information will be pre-tested with patients to ensure appropriate interpretation.

The planned content for each area are described below.

1. *Home Page.*

The objectives of the website and the best way to use it, as well as the research team and contacts, will be presented in the home page. The home page will also provide the opportunity to register for further interactions and contribute to research.

2. *What is osteoporosis? Why should I care?*

In the second area we will provide information about osteoporosis, its causes, risk factors and consequences as well as the epidemiology of the disease. An automatic survey about the knowledge of visitors on osteoporosis will be offered with immediate feedback on correct and wrong concepts.

3. *My probability of suffering a fracture over the next ten years.*

4. *What should I do?*

   a. *Should I seek the help from a health professional?*

   b. *What else can I do to prevent osteoporosis and have healthy bones?*

The third area will have a connection to FRAX®-Port and will allow visitors to calculate their ten years' probability of fracture, with or without bone mineral density (BMD). Visitors will then be linked to the fourth area where they will find recommendations for action according to the fracture probability estimated by FRAX®-Port: Seeking health care and/or adopting self-led osteoporosis prevention strategies including healthy behaviours and prevention of falls. Information will also be provided about the principles of good practice in the treatment of osteoporosis, including the appropriate use of calcium and Vitamin D supplements.

5. *Where can I find more information?*

The fifth area will contain connections to other relevant sites and platforms dedicated to osteoporosis.

6. *Feedback on the web platform. Report of actions taken as a result of its use.*

In the sixth subdivision we will collect information about the impact of the platform on the attitudes and actions of users regarding osteoporosis and their own fracture risk.

7. *Discussion forum for patients, supported by health professionals*

The seventh subdivision will be an open space for discussion among patients and other platform users, which will be facilitated and informed by a health professional team. Users will be invited to present questions to the health care team and a "Frequently Asked Questions" section will be built and provided.

Dissemination Strategies

The full Portuguese-speaking population around the world is eligible to participate in and benefit from the project, totalling around 300 million people. However, the main focus is the population resident in Portugal.

The project includes strategies specifically dedicated to the inclusion of the elderly in order to overcome their limited access to the internet and/or difficulties in reading.

A campaign to promote the website will take place in the entire country, targeting two different age-groups:

- The population at risk (> 40 years)
- The children and grandchildren of people at risk. Activities targeting secondary school and university students will encourage them to use the webplatform and its contents as a gift to their parents and grandparents, while benefiting themselves from the knowledge provided therein.

All financial resources available after building the webplatform and assuring its proper functioning will be devoted to dissemination and recruitment. The following strategies will be considered, depending on cost/resources:

- Web campaign (e-mails, facebook, twitter, students' associations, senior associations, socially active groups and institutions, etc.)
- Participation in TV shows targeting the older population, through Public Relations activities
- Advertising campaign – Newspapers, Outdoors, mailings, radio, television.

Funds will be sought to secure the services of a professional advertising team.

Continuous evaluation and improvement of the project

An automatic questionnaire regarding socio-demographic characteristics of the user (gender, age, education, employment status) and questions about the pertinence and importance of the information provided by the website will be generated whenever the user is about to

leave the platform. Users will be invited to send an automatic e-mail alert to friends and relatives who might be interested in the platform's content.

Permission for a later email contact will be requested so that, after one month, users are enquired about the course of action adopted as a consequence of the previous visit.

The number of accesses to the site, as well as time spent and areas visited, will be monitored and studied. The discussion forum will be managed by a team of health professionals and future qualitative analysis of the discussion will be performed.

The results of the preliminary survey about the knowledge of osteoporosis will be analysed and compared with the feedback given by the participants in the survey done at the end of their visit.

These data will serve as the basis for continuous assessment and improvement of the communication strategies and its targets, through structured quality improvement cycles

Limitations and Potential Problems

The success of this project will depend on the number of visitors and the website ability to engage the user in the proposed activities. A possible limitation of this project is the limited access of the elderly population to the Internet. To this purpose, we intend to launch an awareness campaign targeting adolescents and university students to promote and facilitate the access of their parents and grandparents to the website.

Limitations in funding may hinder our ability to disseminate knowledge and promote the use of the web platform. The Internet social networks may provide the cheapest possible alternative to overcome this problem.

Integration of this educational program within the objectives of a "Fracture Liaison Service" in Direção Geral de Saúde will make a substantial contribution to its sustainability, in a phase where the accessibility to informal funding by pharmaceutical companies is increasingly scarce and difficult.

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Chapter 9

A PROPOSAL FOR THE CREATION OF FRACTURE LIAISON SERVICES (FLS) IN THE NATIONAL HEALTH SYSTEM

The secondary fracture prevention gap

An effective public health response to the increasing burden of osteoporotic fractures requires a complex set of articulated actions, involving health authorities, community and hospital services and must engage patients, carers and specialists from different disciplines and backgrounds.[1]

The occurrence of a fragility fracture represents a uniquely valuable opportunity to introduce preventive interventions for several reasons:

- Fragility fracture is the most visible evidence that the patient has severe osteoporosis
- The patient is in contact with medical services to receive treatment of a consequence of the disease
- All human and technical means need to fully assess the patient as well the disease severity and its origins in order to select the best intervention are immediately available
- Victims of recent fractures and their families are at an especially sensitive moment to adhere to preventive intervention
- Fractures are associated with a higher risk of new occurrences, especially within the first year[2]
- All national and international recommendations establish that patients with osteoporotic fractures should be treated irrespective of other considerations or investigations.[3-5]

Fractures represent a unique opportunity for intervention. It cannot be wasted and yet, it frequently is. An audit performed in 16 Australian hospitals involving 1829 fragility fracture cases[6] found that only 10% percent were appropriately investigated, 12% were commenced on calcium, 12% on vitamin D and a scarce 8% were prescribed bisphosphonates. A population based study in the Netherlands[7] concluded that only about 15% of patients suffering a fragility fracture are prescribed osteoporosis medications in the one year after the fracture. An audit by the Royal College of Physicians (UK)[8] reported that, by 2012, 33% of non-hip fracture and 60% of hip fracture patients received appropriate management for osteoporosis. In the United States a study involving 51436 hip fracture patients admitted to 318 hospitals across the country reported that 6.6% of patients were prescribed calcium and vitamin D supplements, 7.3% received antiosteoporotic agents and only 2% received a combination of these therapies, as recommended.[9]

A recent prospective observational study with more than 60,000 women aged ≥55 years, recruited from 723 primary physician practices in 10 different countries, reported that, one

year after fracture less than 20% of the patients with new fractures had received osteoporosis treatment.[10]

This care gap has also been identified in Portugal: only 4 a 15% of the patients admitted to Portuguese hospitals due to a fragility fracture are discharged with a prescription for osteoporosis.[11-15] We made similar observations in our hospital through a series of studies, which analyzed all emergency episodes of fragility fractures in people above the age of 50 years, in the period from 1st April to 30th June 2013. A total of 330 low-impact fractures were identified: 26 affecting the humerus, 26 the vertebral spine; 49 the leg; 100 the forearm; and 129 the hip.[16-18] One year after the fracture only 25 (7.6%) patients indicated that they had been prescribed any form of antiosteoporotic treatment. Of these, 40% had stopped the therapy prescribed at least once during this period.[16-18] These results mirror a widespread reality at a national level, as reflected by our study described in chapter 5. We obtained data from 186 people who suffered a hip fracture in 2011, from all districts of Portugal, providing a valid representation of the epidemiology of these fractures in our country. The results showed that only 16.7% of these patients had received a prescription of anti-osteoporotic agents and 29.6% a prescription of calcium ± vitamin D, within two years following the fracture.

The fact that our national and regional results are in line with international observations does not make them less regrettable and worrying. This state of affairs represents an intolerable break of responsibility towards patients and their families, as well as a momentous waste of health resources. We take it as our obligation, as health professionals, to contribute to its correction.

The origins of the problem

It has been argued that this problem occurs because orthopaedic surgeons rely on primary care doctors to manage osteoporosis, while primary care physicians feel free of that responsibility, as the bone specialist did not embrace it.[19] Medical specialists typically involved in the treatment of osteoporosis, usually rheumatologists or endocrinologists, do not interact with the patient during the fracture episode.[20] A study in an Academic Centre from the USA revealed that the percentage of patients with a fragility fracture that received antiosteoporotic treatment at discharge was in the range of 45 to 60% when care was provided by Rehabilitation and Medicine departments as opposed to only 12% in orthopedics.[21] It might be argued that the solution should reside in the sensitization of trauma specialists and their education in the biology and treatment of osteoporosis. Although educational programs have been shown to increase the quality of preventive interventions in orthopaedic departments, the effects are generally considered to be short-lived.[22] In fact,

recent recommendations issued conjunctly by the European Societies of Trauma (EFFORT) and Rheumatology (EULAR) do not argue in favor of such a solution. They actually recommend that orthopedic surgeons are supported in the care and prevention of fragility fractures by colleagues of other specialties, namely gerontologists and rheumatologists.[23]

Solutions. The Fracture Liaison Service.

FLSs are increasingly recognized as the most efficacious and best proven solution to close the secondary fracture prevention gap.[1 19 24-27] In 2011, the Fracture Working Group of the International Osteoporosis Foundation (IOF) published a position paper on coordinator-based systems for secondary prevention in fragility fracture patients[19] and established that the Fracture liaison services are the most appropriate strategy to close the secondary fracture prevention care gap[20].

The FLS task is to ensure that all patients presenting with fragility fractures to the particular locality or institution receive fracture risk assessment and treatment as appropriate.[28 29]

From 2000 to 2010, the Glasgow FLS (the first FLS in the world) assessed more than 50,000 consecutive fracture patients. During that period, hip fracture rates in Glasgow were reduced by 7.3% in comparison to an almost 17% increase in England.[30] Ninety-five per cent of people with a wrist fracture in Scotland were assessed and/or treated, compared to 20–25% in centers operating other (or no) methods of secondary fracture prevention.[30]

FLSs have also been proved to be cost-effective.[31-38] A recent health economic analysis established that the Glasgow FLS, in the UK, is actually cost-saving in the prevention of secondary fractures. Compared to usual care in the UK, for every 1,000 fragility fracture patients assessed by the FLS, 18 fractures (including 11 hip fractures) will be prevented, with a cost-saving of €23,350 after taking into account all costs including those of treatments.[31] In the UK, the Department of Health declared that national implementation of FLS, would result in cost savings of up to £8.5 million over 5 years.[19 39]

The implementation of a FLS

The first step in the implementation of a coordinator-based system is to place the concept onto the provider's agenda.[40] The most powerful way to do this is through audit both of the efficiency of the existing osteoporosis service, if there is one, and the reliability of delivery of secondary prevention to fragility fracture patients perhaps starting with an easily retrievable, defined group such as hip fractures.[40] Such review usually identifies; a) disproportionate use of resources (financial, personnel time and DXA scanning) for patients who are fundamentally at very low risk of fracture and b) shockingly low rates of intervention post-fracture (as we did), where the cost-effectiveness of intervention is well documented.[19]

Multidisciplinary support is essential in service innovation and development and step two is therefore to assemble the development team.[41] Examples of the disciplines that might be involved in the development of FLSs are: lead clinician, secondary care clinicians - consultant orthopaedic, rheumatologist, gerontologist; Nurse specialists; Primary care clinicians; Patient representatives; Physiotherapists. This should not obscure that the service must always be patient-centred.

Multidisciplinary engagement in service provision, management and development will ensure that the service evolves in a way that addresses the needs of all interested parties.[1]

Coordinator programs cannot be imposed from outside without internal support. The essence of a coordinator-based system is that it takes the opportunity for secondary fracture prevention directly to the patients without requiring any additional referral process. If the lead clinician is not an orthopaedic surgeon, an agreement with orthopedic department should be established to secure the access to patients.[19 42]

We have started contacts with the Portuguese Society for Orthopaedics and Trauma in trying to lay the grounds for a cooperative program at national and local level towards the establishment of FLSs, involving also the Portuguese Society for Rheumatology and the National Health Authorities.

The operations of an FLS

The identification of patients with a new clinical fracture and assurance of their appropriate management is the fundamental responsibility of an FLS[1]. This is achieved by bringing the trauma department and the departments primarily responsible for osteoporosis treatment together, within a structured care pathway with commonly agreed roles and rules.[19 43] The system is managed by an FLS Coordinator, typically a Nurse Specialist dedicated to this role.[1 26 27] who works to pre-agreed protocols to case-find and assess fracture patients.[43] The coordinator acts as the link between the orthopaedic team, the osteoporosis and falls services, the patient and the primary care physician.[26]

There is a need for a lead clinician to act as a local champion, leading the service development, handling the politics of persuasion, securing funding and leading business case development.[44] The lead clinician should have an ongoing commitment to lead the service, especially if the service is primarily to be delivered by nurse specialists.[45] He should ideally be recruited among consultant endocrinologists, rheumatologists, gerontologists or orthopaedic surgeons. It is essential that the core team includes an orthopaedic surgeon, an insider in the fracture clinic. The key credentials are enthusiasm for the role and having the time to devote to developing and maintaining the new service.[41]

Figure 1 represents a typical workflow on a Fracture Liaison Service.

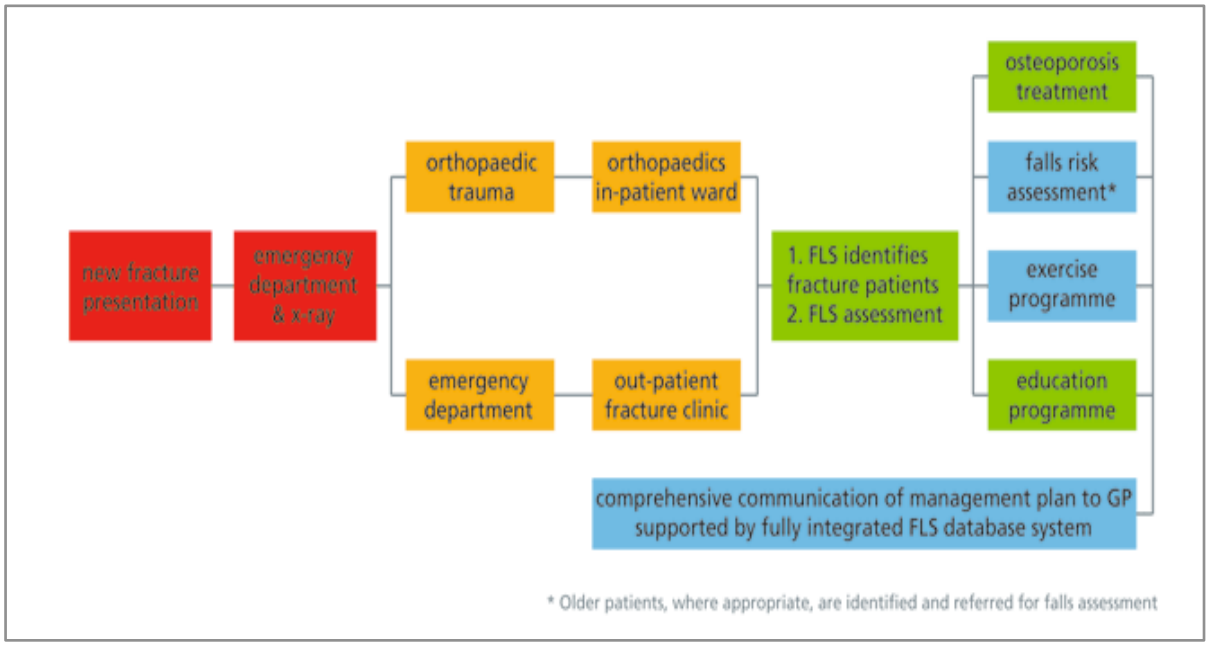

Figure 1. An example of work flow in a Fracture Liaison Service.

Reproduced from Gittoes N, McLellan A, Cooper A. Effective secondary prevention of fragility fractures: clinical standards for fracture liaison services. National Osteoporosis Society, Camerton 2015.[46]

FLSs should recruit all patients aged 50 years and over who have sustained new fractures at any skeletal site, though an exception is justified for fractures of skull, facial, digit and scaphoid bones that are typically traumatic in aetiology.[47] The assessment should occur as soon as feasible after the fracture. In practice, this should ideally be observed within 6–8 weeks after fracture, but no longer than 3 months, as the risk of having a further fracture is higher in the first year following a fracture.[28 47] Patients cared for in the orthopaedic ward should have an assessment by a specialist nurse during the admission. This initial contact is essential to raise awareness of osteoporosis and to invite the patients for their subsequent assessment. This contact also allows the nurse to register the patient in the system and provide written educational materials.[48]

The assessment (protocoled and accepted by all departments involved in the care of these patients) should incorporate fracture risk assessment, evaluation of the risk of falls and, if indicated, dual-energy X-ray absorptiometry (DXA) or other tests to identify underlying causes of secondary osteoporosis.[1] According to the results of these evaluations, a personalized package of care is designed and implemented, including drug treatments and non-pharmacological interventions. Education of patients and their families is always paramount and grounded on patient centered care approach.[19] The management plan, which should be in agreement with local and national guidelines, will seek to engage the patient, family members, primary care physicians and other health professionals involved the long-term management of the patient.[47]

The FLS, served by adequate information systems, will ensure that patients and their care is followed up for sufficient time to guarantee appropriateness and adherence. It is recommended that this evaluation takes place in presence or remotely. The set of data to be collected in every contact should be predefined so as to serve quality of care, audit and continuing research.[19] It is essential that interventions and outcome measures are recorded in an appropriate database. These data can and should be presented to those who provide funding as evidence of service effectiveness and to ensure long-term sustainability. Such evolution requires ongoing engagement with all stakeholders and, crucially, continuous data.[47]

A partnership with Orthopedics department of Centro Hospitalar e Universitário de Coimbra and Rheumatology department was already establish to ensure the creation of the Fracture Liaison Service in our hospital. The candidate will coordinate the service.

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Chapter 10

OVERVIEW AND FUTURE DIRECTIONS

OVERVIEW AND FUTURE DIRECTIONS

In this final chapter we summarize the main findings of the studies presented in this thesis, discuss their relevance and implications in an integrated perspective and explore future perspectives including a research agenda.

This work was designed to lay the scientific foundations for a substantial change in the national standards of practice in the prevention of osteoporotic fractures, both at an individual and public health perspective.

This endeavor was structured around the establishment of the Portuguese version of FRAX®, and derivation of evidence based-strategies for preventive interventions based on absolute fracture risk and cost-effective analyses. The consistency of these measures was significantly reinforced by the demonstration that FRAX® is the best fracture-risk prediction tool available to application in Portugal and that its performance remains high in our specific epidemiological setting.

The selection of FRAX® as the best suited risk prediction algorithm to apply in Portugal was substantiated by the results of a thorough systematic literature review and meta-analyses, whose methodological quality and reliability is indorsed by publication in the highest ranking international rheumatology journal (**Chapter 2**). This work demonstrated that FRAX® had the largest number of externally validated and independent studies (26 studies in 9 countries), followed by Garvan (6 studies in 3 countries) and by QFracture (3 studies, all in UK). FRAX® was considered the instrument that better combines accuracy, applicability, validity and feasibility in clinical practice (QFracture contains 31 items, FRAX® 11, and Garvan only 5).

We developed the Portuguese version of FRAX®, in cooperation with the World Health Organization (WHO) Collaborating Centre for Metabolic Bone Diseases in Sheffield, UK (**Chapter 3**). This work was based on the thorough analysis of nationwide epidemiological data on hip fractures, derived from the National Hospital Discharge Register and mortality rates provided by *Instituto Nacional de Estatística* (Portuguese Statistics Institute). This tool was made available, in Portuguese language, at the official FRAX® website. This allowed, for the first time, the estimation of individual absolute fracture risk based on actual national data, an indispensable resource, given the large inter-country differences in fracture rates. Since its release in September of 2012 and untill 30th September of 2016, 85,126 calculations were performed, representing a mean of near 60 calculations per day in this 4-year period. This demonstrates that the calculation of 10-year absolute risk of fracture has been implemented in the routine practice of health professionals in this field, although further dissemination is needed.

The validity of FRAX® Port was established in a large scale study including ten-year follow-up data from 2626 Portuguese inhabitants, from three national prospective cohorts (**Chapter 4**).

The results robustly demonstrated that the predictive performance of FRAX® in the sample was superior to that of BMD alone for both MOP and hip fractures. The AUC of FRAX® without BMD for was 0.76, 95%CI 0.72–0.79 for MOP fracture and 0.78, 95%CI 0.69–0.86 for hip fracture. No significant improvements were found when BMD was added to FRAX® clinical variables (p=0.25) for prediction of MOP (0.78, 95%CI 0.74–0.82) and hip (p=0.72)(0.79, 95%CI 0.69–0.89) fractures.

This work benefited from the collection of baseline data 8 to 10 years before, but required the direct involvement of the candidate in the collection of follow-up data from 1735 patients from the SAOL and the IPR cohorts. These two cohorts were revitalized by this work and will be the source of continued research.

The validation of FRAX® Port laid the foundation to involve Portugal in the major paradigm change observed in osteoporosis since 1994: the establishment of intervention thresholds based on actual risk of fracture and cost-effective analyses.

This goal required detailed and reliable data on the economic costs, mortality and quality of life impact of osteoporotic fractures in our population, which were not available. To overcome this hurdle, we collected detailed information regarding the abovementioned outcomes, over the two years following a hip fracture (**Chapter 5**). This study, performed in cooperation with expert heath economists, included 186 Portuguese persons, randomly selected in age, gender and geographic strata to represent the actual epidemiology of hip fractures in Portugal. The results showed that each hip fracture costs €13,434 in the first year and €5,985 in the second year, adopting a societal perspective. We estimated the total cost of hip fragility fractures in Portugal at €216 million per year, representing 1.4% of the national heath budget. The impact upon quality of life was estimated at 0.65 prior to fracture, which decreased markedly to −0.18 one month after the fracture, partially recovering to 0.29 one year after the fracture. The deleterious effect of hip fractures on health related quality of life was clear. Within 2 years of follow-up time of this study, 26.9% of patients with hip fracture died. The estimated expected mortality for the general population of similar age and gender composition was approximately 8.6%, providing another alarming indicator of the importance of this problem.

In order to establish cost-effective thresholds for intervention in our population we again partnered with the WHO Collaborating Centre, and recruited the technical support of team of

health economists based in Sweden with extensive experience in the field of osteoporosis (**Chapter 6**). Portuguese data collected as described above was fed into a previously developed and validated state transition Markov cohort model. The analysis allowed the establishment of thresholds for risk-based cost-effective intervention thresholds for four different medications assuming a WTP of 32.000€ per QALY, as recommended by WHO. Our publication has the innovative characteristic of providing the reader with a web-based tool to determine cost-effective threshold for different WTP values and medications.

The scientific evidence accumulated through the work described provided the basis for the elaboration of the multidisciplinary recommendations on DXA request and indication to treat in the prevention of fragility fractures (**Chapter 7**). Thresholds for the rational and cost-effective use of DXA were also established by consensus. This document was endorsed by all Portuguese Scientific Societies with a relevant role in the management of osteoporosis, which will, hopefully, foster its adoption and impact both in clinical practice and in national policy making.

In fact, these recommendations have been adopted by the Portuguese Society for Rheumatology as part of their Recommendations for the Prevention and Treatment of Osteoporosis, now in the final stages of elaboration, with co-authorship by the candidate. They will also form the basis of the National NOC – "*Norma de Orientação Clínica*" (Norm of Clinical Orientation) which will set the national policy for the performance of DXA and for the initiation of pharmacological treatment to prevent osteoporotic fractures.

The methodological issues and limitations of our studies have been openly discussed in the respective chapters. Although research shall always be open to criticism and amenable to improvement, we believe that we have performed state of the art research, following the best and most recent recommendations and quality filters. Taken globally, the research described in this thesis constitutes, we believe, a very coherent and comprehensive body of work and evidence, sufficient to support a much needed paradigm change in the prevention and management of fragility fractures in Portugal. We are very proud that it has received the approval for publication in renowned scientific journals, which suggests its international relevance.

We are equally proud to have contributed significantly to transpose this scientific evidence into clinical practice and heath regulations by means of multidisciplinary recommendations and national practice guidelines. These were the first Portuguese recommendations based on real national data and taking in consideration cost-effectiveness of treatments and interventions. Following these guidelines will certainly promote a more efficient use of human and financial resources in the combat to the ever-growing epidemics of osteoporotic fractures.

In trying to represent our commitment to continue to contribute to further progress in the prevention and management of osteoporotic fractures, we present our immediate plans for future research by means two projects that are already underway, but still without results:

- **The FRAX® Patient project**: A Population-based Osteoporosis Prevention Program using FRAX (**Chapter 8**), aims to increase public awareness about bone health and foster timely and effective intervention using FRAX, through active involvement of the population in osteoporosis screening.
- The **Fracture Liaison Service project** (**Chapter 9**). FLSs are recognized as the most efficacious and best proven solution to close the secondary fracture prevention care gap and constitute an ideal nest to host a persistent clinical and academic effort to contribute to improvement in the scientific understand of osteoporosis as well as the design and implementation of effective prevention and management strategies at individual and population levels.

These two projects will convey and support a more active role for nursing in the prevention and care of patients with osteoporosis and osteoporotic fractures, and could not be developed with all previous work performed by candidate and co-authors. They will provide novel opportunities to demonstrate and reinforce the decisive role that nurses may play in the prevention and management of health issues in the individual and public spheres, by exercising their core competencies of effective communication, critical thinking, strategic planning, program implementation and management. These two projects will also change the role that patients have on the decisions about their health, as they will be based on a patient centered care approach.

Further data regarding osteoporosis in Portugal has been published while we performed this work. A nation-wide study recently performed, EpiReumaPt,[1] indicates that 10.2% of the Portuguese adult population (17.0% of all women and 2.6% of men), report having been diagnosed with osteoporosis. Recent variations in age-specific rates of hip fractures have been related with the economic crisis and the sales of bisphosphonates.[2] An interesting investigation published by Oliveira et al in 2016[3] suggests that Portuguese persons with better socioeconomic status have a lower risk of have a hip fracture RR=0.83 (95%CI 0.65-1.00) and that fluctuations in risk of hip fractures can be related back to the major political and economic events occurred in the first half of the 20th century in Portugal such as the World wars.[4]

An observational study performed in 2014 in Portugal, including 1.587 post-menopausal women, found that 43% had osteoporosis, but only 38.4% had previous knowledge of it and less than a tenth (9.1%) was receiving osteoporosis treatment. In the 12-month period prior to the questionnaire, 12.5% of all women prescribed anti-osteoporotic medication had

stopped it. This decision was driven by patients (61.3%) followed by the physicians (36.2%) and self-reported reasons were economic, polymedication, efficacy, gastrointestinal adverse events and other safety concerns.[5]

This brief overview of recent osteoporosis studies performed by other groups in our country further stress the opportunity and potential reach of the educational, political and medical interventions proposed herein.

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