# Health technology assessment in osteoporosis : new perspectives from adherence and preference studies

# Health technology assessment in osteoporosis:

## new perspectives from adherence and preference studies

Mickael Hiligsmann

2015

The studies presented in this thesis were performed at the School for Public Health & Primary Care (CAPHRI), at Maastricht University.

Part of this dissertation was funded by an unrestricted educational grant from Amgen.

Layout cover & printed by: Gildeprint

ISBN: 978-94-6108-926-7

# Health technology assessment in osteoporosis:

## new perspectives from adherence and preference studies

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit Maastricht op gezag van de rector magnificus Prof. dr. L.L.G. Soete volgens het besluit van het College van Decanen, in het openbaar te verdedigen op woensdag 25 februari 2015 om 14:00

door

Mickaël Hiligsmann

## PROMOTORES

Prof. Dr. A. Boonen

Prof. Dr. C.D. Dirksen

Prof. Dr. T. van der Weijden

## BEOORDELINGSCOMMISSIE

Prof. Dr. E. Wouters (voorzitter)

Dr. B.A. Essers

Prof. Dr. W.F. Lems (VUmc, Amsterdam)

Prof. Dr. A.C. Mühlbacher (Hochschule Neubrandenburg, Germany)

**CONTENTS**

# CHAPTER 1

## GENERAL INTRODUCTION AND OUTLINE

## BURDEN OF OSTEOPOROSIS

Osteoporosis is an increasingly major public health problem. It is a disease characterized by bone fragility and low bone mass, leading to increased fracture risk. In western countries, at least one in three women and one in five men over 60 years will suffer from an osteoporotic fracture during their remaining lifetime [1]. Osteoporotic fractures results in significant morbidity, mortality, and reductions in quality of life [2, 3]. They also double the risk of subsequent fractures [4] and impose a huge financial burden on healthcare systems [5, 6]. In the Netherlands, a recent report by the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA) [5] estimated that approximately 76,000 new fragility fractures were sustained in 2010, comprising 13,000 hip fractures and 12,000 vertebral fractures. The economic burden of incident and previous fragility fractures was estimated at €824 million for the same year. Previous and incident fractures also accounted for 26,300 quality-adjusted life years (QALYs) lost during 2010. Taking into account demographic changes, it was estimated that the number of fractures will increase by 40% in 2025 [5].

Fortunately, several medications are available to reduce the risk of fractures [7]. Oral bisphosphonates (alendronate, risedronate and etidronate) were developed in the 1990s [8, 9] and are still the most widely prescribed medications for the prevention and treatment of osteoporosis worldwide [6]. Several clinical trials and meta-analyses have shown that oral bisphosphonates significantly reduce the risk of non-vertebral and vertebral fractures [10]. Over recent years, new treatment alternatives have become available to prevent and treat osteoporosis, including bazedoxifene, raloxifene, strontium ranelate, oral and intravenous ibandronate, teriparatide, strontium ranelate, subcutaneous injection of denosumab every 6 months and once-yearly intravenous zoledronic acid [7].

## HEALTH TECHNOLOGY ASSESSMENT AND ECONOMIC EVALUATION

With the rapid development of new medications and considering limited healthcare resources available, it is becoming important to help decision makers to allocate healthcare resources and to make appropriate and efficient decisions about the use and reimbursement of osteoporosis medications. Health technology assessment (HTA) aims to assess the medical, social, economic and ethical implications of health technologies and could thus be very useful to inform and guide health policy decisions. In particular, economic evaluations that compare health technologies in terms of costs and outcomes are increasingly used to promote a more rational use of health resources. In the field of osteoporosis, the number of published economic evaluations has markedly increased in recent years [11-13]. In 2007, two systematic reviews [11, 13] were published suggesting that oral bisphosphonates are cost-effective for the prevention and treatment of osteoporosis in women aged over 70 years. In the appraisal of new and existing medications, consideration about their cost-

effectiveness is unavoidably important for decision makers. Understanding and critically appraising evidence about the cost-effectiveness analyses of (new) anti-osteoporosis medications would therefore be very important to help decision makers when prioritizing health technologies, to identify gap in the current evidence and to inform the development of future economic evaluations.

## MEDICATION ADHERENCE

In recent years, the problem of non-adherence with oral bisphosphonates has been recognized as a major obstacle in the treatment of osteoporosis [14]. Several studies have reported poor and suboptimal adherence levels among patients taking oral bisphosphonates [15, 16]. In the Netherlands, it was shown that only 43% of patients treated by oral bisphosphonates are still on treatment after 1 year [17]. Poor adherence with medications leads to reduced effectiveness, higher fracture rates [18] and could potentially have a large impact on the cost-effectiveness of drug therapies. Few studies have however been carried out to assess the economic implications of poor adherence with osteoporosis medications. With the development of new treatments with longer dosing regimens that could potentially improve adherence, as well as behavioural interventions to improve adherence, assessing the economic value of improving adherence would be very worthwhile for decision makers. In addition, reviewing the published literature about interventions and programs to improve adherence would be interesting to inform them about effective interventions to improve medication adherence.

## PATIENTS' PREFERENCES

Alongside medical and economic considerations, insights into the preferences of patients should also be taken into account in policy decisions. The patient's perspective is nowadays becoming increasingly important. Information about what patients need and prefer, and how they value various aspects of a health intervention could indeed be very useful when evaluating healthcare programs [19]. Understanding the preferences of patients, addressing patients' concerns with treatment and involving them in clinical decision-making may also lead to improved adherence [19]. In recent years, discrete choice experiments (DCEs) have been increasingly used to elicit patients' preferences for health care [20, 21]. DCEs can quantify the relative importance of various attributes that characterize a treatment and allow the trade-offs that respondents make between these to be quantified [22]. Some DCEs have been conducted in the field of osteoporosis [23-25] but they did not incorporate preferences for recently introduced routes and timing of administration, which would be very useful for decision makers and clinicians.

## OBJECTIVES OF THE THESIS

The aim of this thesis is to review health technology assessment in osteoporosis and to provide new perspectives from adherence and preference studies.

The aim can be further divided into three objectives:

1. To review evidence about cost-effectiveness of drugs in postmenopausal women and to gain insights into the main drivers of cost-effectiveness ***(Part I – cost-effectiveness studies)***
2. To assess the economic implications of poor adherence with oral bisphosphonates and the economic value of improving adherence, and to review the published literature about interventions to improve adherence ***(Part II – adherence studies)***
3. To evaluate the preferences of patients for osteoporosis medication attributes, and to establish how patients trade between these attributes ***(Part III – preference studies).***

## OUTLINE OF THE THESIS

First of all, ***chapter 2*** provides a general overview of HTA including economic evaluations and reviews the various aspects of HTA in osteoporosis, including epidemiology, and burden of disease, and assessment of the cost-effectiveness of recent advances in the treatment of osteoporosis.

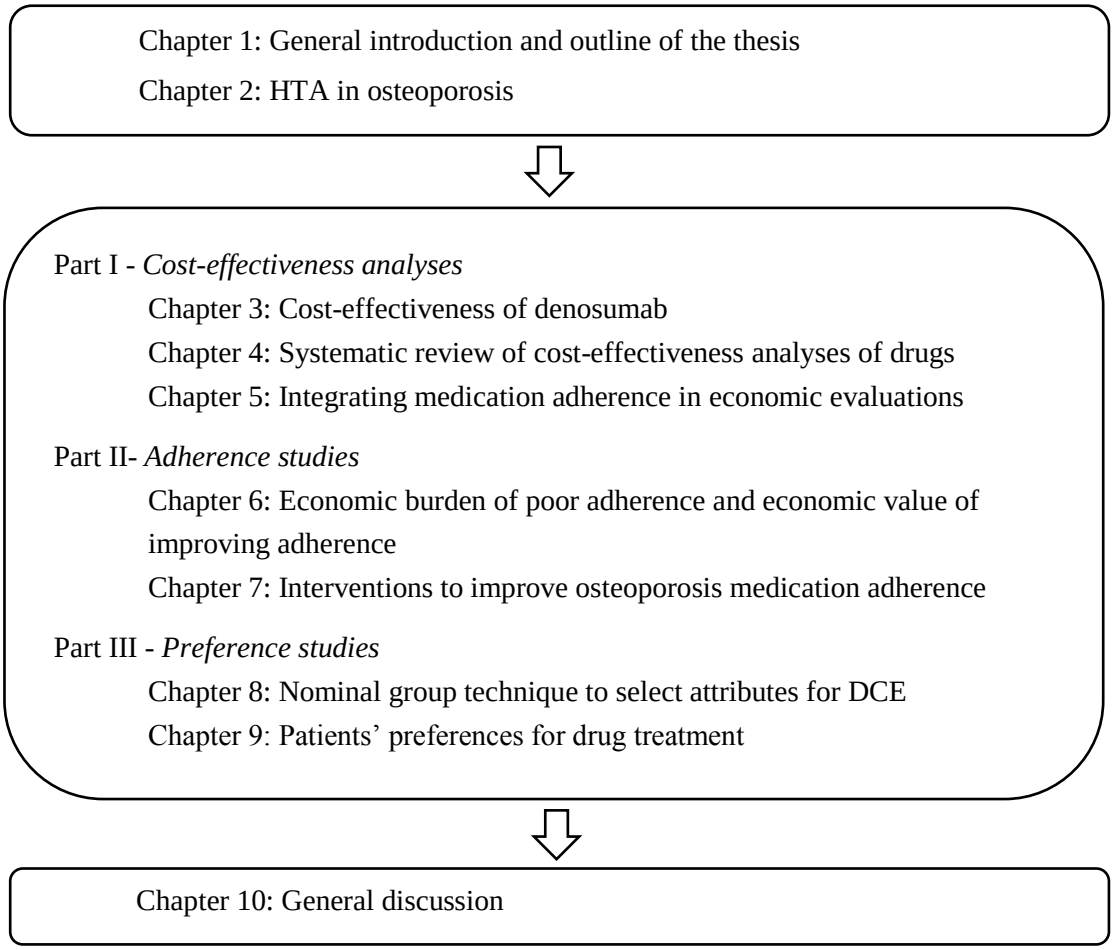
The next three chapters, chapters 3 to 5, are dedicated to answering the first objective of the thesis. More specifically, ***chapter 3*** provides a systematic literature review of published research articles and research abstracts presented at congress about the cost-effectiveness of denosumab, a new (promising) agent for the treatment of osteoporosis. ***Chapter 4*** updates and critically appraises the recent evidence about cost-effectiveness of all available drugs in postmenopausal women and provides insights about the key drivers of cost-effectiveness. ***Chapter 5*** describes and illustrates the importance of integrating medication adherence into economic evaluations in osteoporosis. This chapter forms a bridge between the first two objectives of the thesis.

With regard to the second objective of this thesis, the next two chapters focused on adherence studies. Using a Markov microsimulation model, ***chapter 6*** quantifies the clinical and economic implications of poor adherence with oral bisphosphonates from an Irish setting and investigates the economic value of improving adherence by means of hypothetical interventions. In ***chapter 7***, a systematic review and critical appraisal of interventions to improve medication adherence in osteoporosis is presented.

Chapters 8 and 9 address the development and application of the DCE to cover the third aim of the thesis. ***Chapter 8*** describes and discusses the qualitative research method used to select the attributes for the DCE. ***Chapter 9*** provides the results of the DCE and therefore explains the preferences of patients for osteoporosis medications attributes and how patients trade between these attributes.

Finally, ***chapter 10*** presents the main findings of the thesis and discusses theoretical and methodological considerations. Future directions for research are also addressed.

**Figure 1**| *Outline of the thesis*



## REFERENCES


1. Hiligsmann M, Bruyere O, Ethgen O, Gathon HJ, Reginster JY. Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women. Bone. 2008;43(6):991-4.
2. Lips P, van Schoor NM. Quality of life in patients with osteoporosis. Osteoporos Int. 2005;16(5):447-55.
3. Haentjens P, Magaziner J, Colon-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med. 2010;152(6):380-90.
4. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15(4):721-39.
5. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, 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.
6. Svedbom A, Hernlund E, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: a compendium of country-specific reports. Arch Osteoporos. 2013;8(1-2):137.
7. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24(1):23-57.
8. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280(24):2077-82.
9. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11(1):83-91.
10. Cranney A, Tugwell P, Zytaruk N, Robinson V, Weaver B, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocrine reviews. 2002;23(4):524-8.
11. Fleurence RL, Iglesias CP, Johnson JM. The cost effectiveness of bisphosphonates for the prevention and treatment of osteoporosis: a structured review of the literature. Pharmacoeconomics. 2007;25(11):913-33.
12. Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. Osteoporos Int. 2014;25(1):51-60.
13. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis--a review of the literature and a reference model. Osteoporos Int. 2007;18(1):9-23.
14. Silverman S, Gold DT. Compliance and persistence with osteoporosis medications: a critical review of the literature. Rev Endocr Metab Disord. 2010;11(4):275-80.
15. Rabenda V, Hiligsmann M, Reginster JY. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. Expert Opin Pharmaco. 2009;10(14):2303-15.

16. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporosis Int. 2010;21(11):1943-51.
17. Netelenbos JC, Geusens PP, Ypma G, Buijs SJE. Adherence and profile of non-persistence in patients treated for osteoporosis-a large-scale, long-term retrospective study in The Netherlands. Osteoporosis Int. 2011;22(5):1537-46.
18. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RMC, Silverman SL. Impact of Osteoporosis Treatment Adherence on Fracture Rates in North America and Europe. Am J Med. 2009;122(2):3-13.
19. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health. 2011;14(4):403-13.
20. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ. 2012;21(2):145-72.
21. Marshall D, Bridges JF, Hauber B, Cameron R, Donnalley L, Fyie K, et al. Conjoint Analysis Applications in Health - How are Studies being Designed and Reported?: An Update on Current Practice in the Published Literature between 2005 and 2008. Patient. 2010;3(4):249-56.
22. Ryan M. Discrete choice experiments in health care. BMJ. 2004;328(7436):360-1.
23. Darba J, Restovic G, Kaskens L, Balbona MA, Carbonell A, Cavero P, et al. Patient preferences for osteoporosis in Spain: a discrete choice experiment. Osteoporos Int. 2011;22(6):1947-54.
24. de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Pols HA, Koes BW, Steyerberg EW. Patients' preferences for osteoporosis drug treatment: a discrete choice experiment. Osteoporos Int. 2008;19(7):1029-37.
25. Fraenkel L, Gulanski B, Wittink D. Patient treatment preferences for osteoporosis. Arthritis Rheum. 2006;55(5):729-35.

# CHAPTER 2

## HEALTH TECHNOLOGY ASSESSMENT IN OSTEOPOROSIS

**Hiligsmann M**, Kanis JA, Compston J, Cooper C, Flamion B, Bergmann P, Body JJ, Boonen S, Bruyere O, Devogelaer JY, Goemaere S, Kaufman JM, Rozenberg S, Reginster JY

*Calcified Tissue International, 2013, 93(1), 1-14*

## ABSTRACT

We review the various aspects of health technology assessment in osteoporosis, including epidemiology and burden of disease, and assessment of the cost-effectiveness of recent advances in the treatment of osteoporosis and the prevention of fracture, in the context of the allocation of healthcare resources by decision-makers in osteoporosis. This article was prepared on the basis of a symposium held by the Belgian Bone Club and the discussions surrounding that meeting, and is based on a review and critical appraisal of the literature. Epidemiological studies confirm the immense burden of osteoporotic fractures for patients and society with lifetime risks of any fracture of the hip, spine and forearm of around 40% for women and 13% for men. The economic impact is also large, for example, Europe's six largest countries spent €31 billion on osteoporotic fractures in 2010. Moreover, the burden is expected to increase in the future with demographic changes and increasing life expectancy. Recent advances in the management of osteoporosis include novel treatments, better fracture risk assessment notably via fracture risk algorithms, and improved adherence to medication. Economic evaluation can inform decision-makers in healthcare on the cost-effectiveness of the various interventions. Cost-effectiveness analyses suggest that the recent advances in the prevention and treatment of osteoporosis may constitute an efficient basis for the allocation of scarce healthcare resources. In summary, health technology assessment is increasingly used in the field of osteoporosis and could be very useful to help decision-makers efficiently allocate healthcare resources.

## KEYWORDS

Burden of disease, cost-effectiveness, economic evaluation, health technology assessment, osteoporosis.

## INTRODUCTION

Osteoporosis is a major cause of fracture worldwide, most notably of the hip, spine, and forearm. Osteoporotic fracture is strongly associated with morbidity, especially in terms of pain and disability. Hip and vertebral fractures are also associated with high mortality in the 2 years after the event [1, 2]. Osteoporosis is a common disease and is associated with a substantial healthcare burden. In western countries, one in two women and one in five men over the age of 50 years will experience an osteoporotic fracture during their remaining lifetime [3, 4]. Heterogeneity in hip fracture risk is observed around the world [5], with estimates of a lifetime risk at the age of 50 years that vary from 1% in women from Turkey to 28.5% in women from Sweden [6]. The worldwide direct and indirect annual costs of hip fracture in 1990 were estimated at US$35 billion, with further increases predicted over the next 50 years [7]. In six major European countries, the burden of osteoporotic fractures was estimated in 2010 at €31 billion [8]. Fortunately, there is currently an array of diagnostic tools and effective treatments available for the management of osteoporosis [9].

Considering the limited healthcare resources available, alongside major recent innovations in the management of osteoporosis, it is becoming increasingly important to allocate healthcare resources appropriately and efficiently. Health technology assessment (HTA) aims to evaluate the clinical, economic, social, and ethical implications of the prevention and treatment of a condition—in this case osteoporotic fracture—to guide national healthcare policies (for example, reimbursement decisions). The principal aim of HTA is to form a bridge between scientific experts in clinical practice and decision-makers in healthcare, in order to make the most appropriate use of available strategies for prevention and management. The ultimate target is evidence-based prioritization of national needs for healthcare technology—be it for the prevention of fracture itself or management post-fracture—for optimization of public health initiatives. It was against this background that the Belgian Bone Club held a symposium to explore the issue from the clinician's point of view. This paper was prepared on the basis of the presentations and discussions surrounding that meeting, as well as review and critical appraisal of the literature. Our aim was to discuss the various aspects of HTA in osteoporosis, including epidemiology and estimation of the burden of disease, and assessment of the cost-effectiveness of the recent advances in the management of osteoporosis.

## HEALTH TECHNOLOGY ASSESSMENT

According to the International Network of Agencies for Health Technology Assessment [10], HTA is the systematic evaluation of "the medical, social, ethical and economic implications of development, diffusion, and use of health technology." Its purpose is to support healthcare decisions and inform policy-making through objective information at local, national, or international levels. The aim of HTA is to improve the quality of care by promoting an appropriate and rational use of

healthcare technologies [11] and by facilitating the introduction and dissemination of new technologies.

Health technology includes not only drugs, medical equipment, and devices, but also prevention, diagnostic, and treatment procedures. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks and draw from a variety of methods [10]. This field of research was developed in the 1970s and 1980s in the USA and Europe, and has spread to the rest of the world over the last two decades [12]. HTA government agencies are now operating in many countries. They have been established to provide advice to governments and address, at the national level, the containment of healthcare costs and the assessment of the impact of new technologies [13]. The organization of HTA and its influence on the public policy-making process can vary markedly between countries [14]. In addition, many research institutions are concerned with HTA [15], for example, the National Health Service Centre for Reviews and Dissemination in the UK. In 2012, the International Network of Agencies for Health Technology Assessment consisted of 53 members from 29 countries [10].

HTA is increasingly used by regulatory agencies to authorize a drug, device, or technology for market or reimbursement. HTA can be used to support decision-making by clinicians and patients. It may also be used by other bodies, for example, associations of health professionals, hospitals (for acquisition of new technologies), and companies (to aid product development and marketing decisions) [16].

## EPIDEMIOLOGY AND BURDEN OF OSTEOPOROSIS

The first step of HTA is to assess the epidemiology and burden of the disease or outcome concerned. Epidemiological studies performed in the early 1990s in white North American individuals aged over 50 years indicated that the lifetime risk for any fracture of the hip, spine, or forearm was 40% in women and 13% in men [17]. Similar rates of fracture were reported in a study performed 10 years later in the UK General Practice Research Database (GPRD), with values of 53% for women and 21% for men [18]. These data include fractures not linked to osteoporosis, such as those of the skull, hands or fingers, and ankles or toes. Lifetime risk for fracture of the hip, spine, and wrist has been estimated as 14%, 28%, and 13%, respectively, for women in the UK, and 3%, 6%, and 2% for their male counterparts [7]. The risk of fracture rises progressively from the age of 50 years, and there is a substantial female excess at all-time points above that age.

Fracture rates are known to vary considerably according to geographical location [5], which also influences HTA. Age-standardized incidences of hip fractures are currently available in 63 countries [5]. The age-standardized incidence of hip fracture in Europe and North America is generally higher than in Asia and Africa, and there is also a large difference within Europe (763 per 100 000 women in Norway versus 418 per 100 000 women in England) [19]. These differences

correlate weakly with latitude [20], activity [21], and fall risk [19, 22], but not with bone mineral density (BMD). Geographical differences may be partly explained by time trends. Age, period, and birth cohort all impact on secular trends in hip fracture [23, 24], suggesting that there are determinants that operate throughout life; for example, even maternal vitamin D status may play a role [25].

Data are available regarding incident trends in hip fracture from around 1928 up to the present. Steep and statistically significant increases in age-adjusted rates among men and women were observed in the middle to late 20th century. However, whilst global projections for hip fracture in the 1990s suggested sustained increases due to demographic changes in populations [26], there is evidence that the trends in incidence are reaching a plateau, or may even have declined. This trend is most consistent in the USA, where hip fracture rates and subsequent mortality are declining (though with coincident increase in morbidities associated with hip fracture) [27]. There is also evidence for similar trends in Europe and Oceania, but not (for the time being) in Asia [28, 29]. In Belgium, the age-standardized incidence of hip fracture fell from 5.60 per 1000 women aged over 50 years in 2000, to 5.22 per 1000 in 2007 [30]. These data (excluding readmissions) also highlight a reversal of the secular trend for hip fracture in Belgian women, with a 1.1% reduction in the average yearly change in the incidence of hip fractures in the period 2000 to 2007 [30], compared with a 2.1% increase reported between 1984 and 1996 [31]. The reasons for this reversal are not entirely clear, though it could be linked to changes in risk factors [28], most notably those acting in later life; for example, changes in patterns of physical activity, vitamin D insufficiency, and increasing survival of the frailest elderly were likely to contribute to the rise in hip fracture incidence in the second half of the century. On the other hand, reduction in rates of hip fracture in the last two decades may be linked to wider use of osteoporosis treatments—and some studies have revealed the recent decrease in hip fracture incidence coincided with increased use of osteoporosis treatments [27, 30, 32]—as well as other possible factors, such as increased rates of obesity or improvements in nutrition or tobacco consumption. However, there is no single explanation, and no causal relationship can be ascertained between the increase in the use of osteoporosis medications and the decrease in hip fracture incidence [30, 33]. Further research is necessary to explore these trends in more depth. Despite a reduction in age-adjusted incidence in many countries, the absolute number of fractures is still increasing due to the aging of the population and increasing life expectancies. In Belgium, for example, the absolute number of hip fractures increased by 9% between 2000 and 2007 [30].

A report launched by the International Osteoporosis Foundation (IOF) in collaboration with the European Federation of Pharmaceutical Industry Associations (EFPIA) has revealed the immense burden of osteoporotic fracture [8]. For the year 2010, approximately 2.5 million new fractures occurred in Europe's five largest countries (France, Germany, Italy, Spain, UK) and Sweden alone

[8]. The economic impact of these fractures was estimated to be nearly €31 billion in that year [8]. Approximately 34 000 deaths were causally related to these fractures and the burden expressed in quality-adjusted life years (QALYs) was estimated at 850 000 QALYs. Considering current trends in demography, the burden of osteoporosis is expected to further increase in the near future. The projected number of fractures in these major countries is 3.2 million by 2025, an increase of 29% [8].

## RECENT ADVANCES IN THE TREATMENT OF OSTEOPOROSIS

The diagnosis and treatment of osteoporosis is rapidly evolving. A variety of new treatments for osteoporosis has become available over the past few years [34]. Fracture risk assessment is increasingly used to guide treatment decisions [35], and the impact of non-adherence with osteoporosis medications on treatment efficacy has led to the development of behavioural interventions to improve adherence [36, 37]. The assessment of these major advances from a clinician's point of view is provided below, while the economic assessment will be discussed later.

### *NOVEL TREATMENT STRATEGIES*

Over recent years, new treatment strategies have become available to prevent and treat osteoporosis, including bazedoxifene [38], denosumab [39], ibandronate [40], strontium ranelate [41], and zoledronic acid [42]. Other promising drugs are currently in development, such as odanacatib (a specific inhibitor of the osteoclast protease cathepsin K) and antibodies against the sclerostin and dickkopf-1 proteins [34]. Systematic review of the clinical efficacy, effectiveness, and side effect profiles of these drugs is a crucial part of HTA. Good-quality systematic reviews of the evidence for the efficacy and safety of these drugs are available [9, 34, 43-46], and will not be discussed further here.

### *FRACTURE RISK ASSESSMENT*

Evaluation of risk and prediction of outcome is another important component of HTA. It is well established that BMD is inversely related to fracture risk [47]. For every 1.0 SD decrease in BMD at the hip, spine, or radius, there is an approximately 1.5- to 2-fold increase in fracture risk at any site. Measurement of BMD is therefore an integral part of the prediction of fracture risk. However, there are a host of other clinical risk factors that can improve fracture risk prediction, notably because they increase fracture risk in a manner that is at least partially independent of BMD. Examples are a prior history of fragility fracture, a parental history of hip fracture, current smoking, high alcohol intake, systemic glucocorticoids, and the presence of rheumatoid arthritis [48]. Fracture risk prediction algorithms have been generated to combine results of BMD assessment with the presence of clinical risk factors, thereby improving the prediction of osteoporotic fracture.

Current fracture risk algorithms generally produce estimates of 10-year risk of fracture. The most widely used is the World Health Organization (WHO) fracture risk assessment tool, FRAX®, which is recommended by guidelines in North America, Europe, and Japan. The FRAX algorithm was developed using international population-based data for men and women aged 40 to 90 years. FRAX combines 11 parameters of risk (femoral neck BMD, age, sex, body mass index, prior fracture, parental history of hip fracture, rheumatoid arthritis, glucocorticoids, smoking, alcohol, and secondary osteoporosis) to calculate a 10-year probability for major osteoporotic fracture and for hip fracture [35]. Other fracture risk prediction algorithms have also been produced which are not based on probability (i.e. do not incorporate the death risk), and are less widely used [49-51]. A simpler score, produced by Ensrud et al, used a USA-based population of women aged 65 years or older to determine a 10-year risk of major osteoporotic or hip fracture using the risk factors of age and previous fractures with and without BMD. They considered that this simpler model may predict risk as well as the more complex FRAX algorithm [49], but this is the subject of some debate [52]. The Garvan Fracture Risk Calculator includes BMD, age, sex, previous fracture, and falls to produce 5- and 10-year risks of any fracture in men and women aged over 60 years [51]. Finally, the Qfracture algorithm employs multiple risk factors, including comorbidities, medications, and falls, but not a prior fracture or BMD, to estimate 2-, 5-, and 10-year risks of hip, wrist, and vertebral fracture [50].

The FRAX algorithm is the most widely used tool, and has been endorsed by international guidelines. However, it does have a number of limitations; for example, it only allows for inclusion of femoral neck BMD, but not BMD values at other sites. Moreover, FRAX does not incorporate the notion of dose-response for some of the risk factors, for example, previous fracture and glucocorticoids [53]. Simple guidance for the adjustment of fracture probabilities on the basis of exposure to glucocorticoids and information on lumbar BMD are available [54, 55]. FRAX, like all the models except QFracture (which ignores all previous fracture), may also underestimate risk if previous vertebral fractures are not accounted for, despite established evidence for the influence of incident fracture. Moreover, it does not formally take into account the number of previous fractures. The recent observational cohort study GLOW (Global Longitudinal Study of Osteoporosis in Women) collected information on 50 000 women in 10 countries [56]. Compared with women with no previous fracture, the hazard ratio for incident fracture was 1.81 (95% confidence interval [CI], 1.66–1.97) in patients with one prior fracture, 2.98 (95% CI, 2.63–3.38) with two prior fractures, and 4.80 (95% CI, 4.11–5.60) with three prior fractures [56]. Similarly, the presence of undiagnosed vertebral fracture was associated with a substantially increased risk for hip and new vertebral fracture [57], but could only be incorporated in risk prediction algorithms by systematic evaluation of spinal radiographs. Clearly, this is not feasible for all consultations, though possible indications

for vertebral imaging in fracture assessment should include low BMD, height loss, kyphosis, pain suggestive of a vertebral fracture, previous non-vertebral fracture, and reduced rib-to-pelvis distance. One potential drawback to FRAX may be that it does not include falls, which clearly contribute to the occurrence of fracture and are included in other risk tools [50, 51]. Although there is some evidence that including falls into FRAX would improve fracture risk prediction [58], the incorporation of falls into FRAX may be problematic for a number of reasons discussed elsewhere [53].

In conclusion, FRAX and other fracture risk algorithms enable fracture prediction based on clinical risk factors with or without BMD and provide a basis for setting intervention thresholds. Current strategies for external validation and comparisons of fracture risk algorithms involve procedures of discrimination, calibration, classification, and decision curve analysis, all of which have drawbacks and require further study [52].

### *ADHERENCE TO TREATMENT*

The problem of medication non-adherence has emerged as a critical hurdle to osteoporosis management. Adherence with osteoporosis medications is poor and suboptimal [59-61]. Several studies have suggested that between 50% and 75% of women who initiate oral bisphosphonate therapy are non-adherent within 1 year. Poor adherence reduces the effectiveness of osteoporosis treatment, resulting in lower BMD gains and subsequently higher fractures rates [62, 63]. Approximately 50% of the potential clinical benefits of oral bisphosphonates are lost due to non-adherence [36, 37, 64] and the costs per QALY from these medications are doubled when assuming non-adherence [64]. Non-persistence is the leading problem with adherence, with more than 90% of the clinical and economic burden of poor adherence resulting from non-persistence [64].

Over the past few years, behavioural interventions and treatments with longer intervals between doses have been developed in order to improve medication adherence. Systematic reviews of these interventions identified a limited number of studies of variable quality suggesting that some intervention techniques may help improve medication adherence, but this requires further investigation [65, 66]. Different dosing regimens [67], the use of a decision aid [68], and education programs [69] may also improve medication adherence.

## ECONOMIC EVALUATION

Economic evaluation is as important a branch of HTA as the epidemiological and treatment aspects. The aim of economic evaluation is to examine outcomes and costs of healthcare interventions; it could be defined as the comparative analysis of two or more healthcare interventions in terms of both costs and impact on outcomes [70]. By informing decision-makers about the relative cost-effectiveness of different healthcare interventions, economic evaluation can help decision-makers

make rational decisions and efficiently allocate resources. Cost-effectiveness is currently considered to be the fourth hurdle in drug development, behind quality, safety, and efficacy [71]. Although the most common application of economic evaluation is drug pricing and reimbursement [72], the implementation and viability of any other health intervention (such as screening or information campaigns) also depend on their evaluation and their relative cost-effectiveness.

With the rising demand for healthcare, budget constraints, and the rapid development of health technologies, economic evaluation plays an increasingly large role in the decision-making process for healthcare interventions. This has led to an increase in the number of published economic evaluations in the literature and to an increased use of economic data in the healthcare decision-making process (in particular, for drug reimbursement). Many countries currently require economic evaluation as part of the reimbursement process for drugs [73].

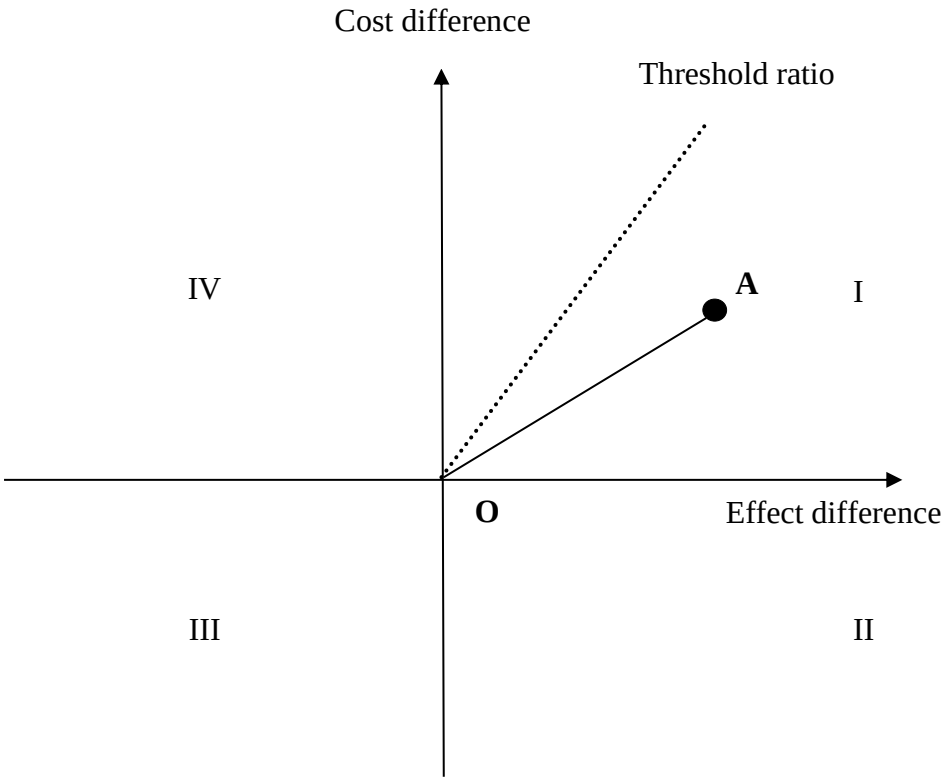
The four main types of economic evaluation all approach costs in the same way, but differ in the way they approach outcomes [70]:

- *Cost-minimization analysis* is used where the consequences of two or more interventions are broadly equivalent, and so the difference between them is limited to a cost comparison. This approach is only meaningful for agents with similar efficacies or side effects, which is difficult to apply to a heterogeneous class like the osteoporosis drugs [74].
- *Cost-benefit analysis* measures both costs and benefits in monetary terms. This approach aims to demonstrate that a program will yield to a net welfare gain, and ranks interventions according to the net benefit they provide. The practical difficulties of measurement and valuing health benefits have limited the use of this type of analysis in healthcare [75].
- *Cost-effectiveness analysis* (CEA) compares costs and outcomes expressed in a single dimension, such as fracture saved, BMD gained, or life-years gained.
- *Cost-utility analysis* (CUA) is considered as a specific case of CEA where the outcome measure is expressed in QALYs. The QALY estimator is an attractive outcome measurement in the field of osteoporosis because it offers the advantage of simultaneously capturing the benefits from a reduction in mortality and from a reduction in morbidity [76]. In addition, this approach allows comparison across different health programs and diseases by using a generic unit of measure.

There are different categories of costs that may or may not be included in an economic evaluation. It is essential to specify and justify the perspective in which the analysis is undertaken. The most common perspectives used are those of healthcare payers and society. The societal perspective is the broadest, including direct and indirect medical costs, and is theoretically preferred [70]. However, most local guidelines recommend the use of a healthcare payer perspective [73].

The results of a CEA or CUA are usually expressed in terms of the incremental cost-effectiveness ratio (ICER), which is defined as the difference in terms of costs between two interventions divided by their difference in effectiveness. An ICER represents the additional cost of an intervention per effectiveness unit (for example, fracture saved or QALY gained) versus the comparator. The results can be presented graphically on the cost-effectiveness plane (Figure 1), where the difference in effectiveness between intervention A and comparator O is represented on the horizontal axis, and the difference in cost on the vertical axis [77]. If A is located in quadrants II or IV, the choice is straightforward: in quadrant II, intervention A is more effective and less costly than comparator O, and said to be dominant; in quadrant IV, intervention A is less effective and more costly than O, and should be rejected. In quadrants I and III, there is no obvious decision; intervention A is either more effective and more costly than comparator O (quadrant I), or less effective and less costly (quadrant III). The choice will depend on the maximum amount the decision-maker is willing to pay (or accept) for a unit of effect (for example, a fracture prevented or a QALY). The slope of the line between intervention A and comparator O is the ICER. As shown in Figure 1, if intervention A falls below the ICER threshold, then it is deemed cost-effective.

**Figure 1**| *Cost-effectiveness plane*




*The difference in QALYs between intervention **A** and comparator **O** is represented on the horizontal axis, and the difference in cost on the vertical axis. The slope of the line between intervention **A** and comparator **O** is the incremental cost-effectiveness ratio (ICER). If **A** is located in quadrants II or IV, intervention **A** is dominant (more effective and less costly than comparator **O**), in quadrant IV, intervention **A** is less effective and more costly than **O**. In quadrants I*

*intervention **A** is more effective but more costly and in III less effective and less costly. The choice will depend on the cost-effectiveness threshold that represents the maximum amount the decision-maker is willing to pay for a unit of effectiveness. Interventions that fall below the cost-effective threshold would be deemed cost-effective.*

In order to draw conclusions about an intervention's cost-effectiveness, ICER should be compared with a cost-effectiveness threshold, above which the intervention would be deemed not cost-effective (because the additional cost for an additional unit of effect is too high) and below which it would be deemed cost-effective. The UK currently uses a threshold of £20 000 to £30 000 per QALY gained [78], though most other countries define no generally accepted or recommended thresholds for cost-effectiveness. The objections to the specifications of a fixed cost-effectiveness threshold are numerous. First, any threshold for cost-effectiveness would be somewhat arbitrary and would be variable over time. A threshold would also vary between countries to reflect differences in resources. The WHO has suggested a cost-effectiveness threshold based on evaluating each disability-adjusted life-year (DALY) as three times the gross domestic product (GDP) per capita [79]. On this basis, a willingness-to-pay of two times GDP per capita was used to define intervention thresholds in osteoporosis [80, 81]. In addition, healthcare decision-making remains a multifactorial process and depends on many factors other than cost-effectiveness. As decisions are not solely based on ICER, it is probably not necessary to define a fixed threshold below which an intervention can be considered cost-effective. This should, however, not be used as an argument against the use of economic considerations in healthcare [82]. In most countries, interventions with a low ICER have a higher probability of being adopted/accepted than those with a high value [82, 83]. Factors to considered alongside cost-effectiveness include burden of disease, uncertainty regarding cost-effectiveness, lack (or inadequacy) of alternative treatments, and overall financial implications for government [84]; the seriousness of the disease and equity objectives are also important. Recently, the UK National Institute for Health and Clinical Excellence (NICE) introduced new criteria and increased the threshold for end of life treatments [85].

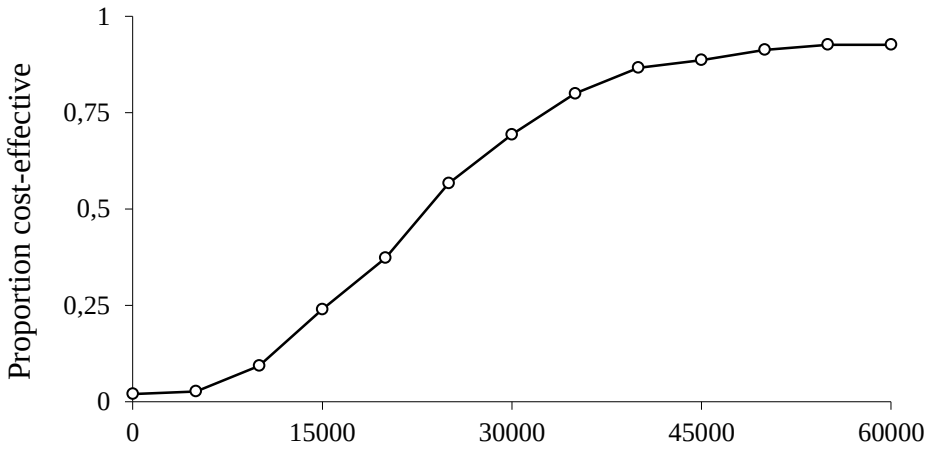
Economic evaluation can be performed alongside randomized controlled trials [86] or separately using decision-analytic modelling [87]. The first approach estimates costs, effects, and utilities using individual patient data [88], but suffers from a number of limitations that reduce its usefulness in informing decision-makers about the economic value of interventions. These include, for example, a failure to compare with all relevant options, a truncated time horizon, and a lack of relevance of the decision context [89]. In addition, reliance on a single trial may ignore results from other clinical trials, meta-analyses, and observational studies [87]. Decision-analytic models are therefore becoming a necessary feature for estimating the economic value of health interventions. This is especially true in osteoporosis since the prevention of an osteoporotic fracture (in particular of the hip or vertebra) has long-term consequences on costs and outcomes that may not be captured by trial data.

Healthcare modelling involves the application of mathematical techniques to summarize available information about healthcare processes and their implications [90], usually with computer software. A model aims to represent the complexity of the process in a simple and comprehensible form [91]. Modelling is useful to extrapolate beyond clinical trials, to combine multiple sources of evidence, to incorporate epidemiological, clinical, and economic data, and therefore to answer more relevant policy questions [90]. In addition, modelling is also appropriate at the early stages of the development of a new technology to inform research priorities prior to initiation of clinical trials [90, 91].

There may be some problems with using modelling in the economic evaluation of healthcare [92]. Inappropriate use of modelling could lead to unreliable conclusions, as would be the case for combination of evidence from incompatible studies with a high degree of uncertainty, and oversimplification of some aspects of reality [88, 90]. Manipulation could also be greater when modelling reflects commercial and government interests [93]. An example is the discussion about the appraisal of NICE on the health economic assessment of interventions for the primary and secondary prevention of osteoporotic fractures in postmenopausal women in the UK [94]. Some authors do not support the view of the NICE guideline and doubt the validity of the model and the appropriateness of the use of the model to inform its guidance [95]. Interestingly, a recent study has shown that funding source (industry versus non-industry) did not seem to significantly affect the reporting of low or high ICERs for bisphosphonates [96].

Models are only as good as their ability to represent the real world. In order for the results and conclusions of economic evaluation to be reliable and valid, it is crucial that the model and the data both represent the reality of the disease as accurately as possible. Guidelines have been developed to increase the quality and reliability of modelling [73, 97]. These include the characterization of uncertainty using appropriate statistical approaches. There could be a substantial amount of uncertainty in the model parameters (and assumptions), and this should be explored using univariate and probabilistic sensitivity analyses. Univariate sensitivity analyses assess the impact of single parameters on the results (which can be represented as a tornado diagram [98]), while probabilistic sensitivity analyses examine the effect of the joint uncertainty surrounding the model variables. Cost-effectiveness acceptability curves (CEAC) can then be constructed to show the probability that the intervention is cost-effective compared with the alternative, for a range of decision-maker's willingness-to-pay thresholds. An example is shown in Figure 2. CEAC has been widely adopted to represent uncertainty in cost-effectiveness analyses [99].

**Figure 2**| *Example of a cost-effectiveness acceptability curve*




*This graph shows the probability of an osteoporotic treatment being cost-effective compared with no treatment in patients aged 70 years with prevalent vertebral fractures, as a function of the decision-maker's willingness-to-pay per one QALY [108]. The curve was estimated from probabilistic sensitivity analyses where most parameters (such as therapeutic effect, fracture risk, cost, and disutility) were assigned a probability distribution (e.g. normal or uniform distribution) and values from each distribution were randomly selected during a predefined number of simulations.*

Economic evaluations conducted in the field of osteoporosis are usually based on so-called Markov state-transition models [76]. Markov models are particularly appropriate when a decision problem involves a continuous risk over time, when the timing of events is important, and when events may happen more than once [100], which is the case for osteoporosis. In a Markov model, a cohort of patients is followed over time along mutually exclusive health states (such as healthy, fracture states, and death). At the end of a cycle, patients can move to another health state according to transition probabilities. Values (typically cost and utilities) are assigned to each state and expected values are then obtained by summing costs and utilities across health states, weighted by the proportion of patients in each state, and then summing across cycles [77]. To assess Markov models, either cohort or individual simulations can be carried out. A microsimulation model follows one individual at a time throughout the model. Due to the probabilistic structure of the model, there will be random variation in individual outcomes (called first-order uncertainty) [101], which can be reduced by simulating a large number of patients. The major advantage of microsimulation is that a full patient history is recorded, which increases the reliability of the results and is currently largely compatible with existing state-of-the-art, evidence-based literature [101]. The weakness of such models is that they require more sophisticated and detailed data than cohort-based models. This fact was invoked as a rationale for remaining with cohort modelling approaches in osteoporosis [76].

## ECONOMIC EVALUATION IN OSTEOPOROSIS

With limited healthcare resources, increasing awareness of osteoporosis, and new diagnostic tools and effective treatments, economic evaluation is increasingly widespread to help decision-makers allocate resources in osteoporosis. The number of published economic evaluations in osteoporosis has therefore markedly increased over recent years [76, 102-104]. They have mainly concerned treatment [76, 105, 106] and screening strategies [102, 107]. Recent advances in the diagnosis and treatment of osteoporosis have provided new insights and challenges for economic evaluation that will be discussed below.

### *ECONOMIC EVALUATION OF NEW OSTEOPOROSIS TREATMENTS*

As many countries now require economic evaluation as part of the submission file for drug reimbursement, novel drug treatments have been the subject of many economic analyses. Osteoporotic treatments are usually cost-effective in women aged over 60 or 70 years with low bone mass, especially those with prior fractures [76, 104, 105]. In osteoporotic women aged over 80 years, drug therapies are generally reported to be cost-saving [108, 109], meaning that the cost of treating these patients is lower than the averted costs resulting from prevented fractures.

With the development of new products, the question of relevant comparators arises. Health economic evaluations should ideally compare a new intervention with the interventions it is likely to replace. In osteoporosis, there is a lack of head-to-head comparisons, which has led to a paucity of ICER comparisons between active treatments [110]. No treatment (or calcium and vitamin D supplement) appears as the most widely used comparator [76]. Cost-effectiveness analyses often replicate both arms of clinical trials (higher level of evidence) when active treatment is compared with placebo. It has also been argued that the current standard of care is no treatment, since osteoporosis is an undertreated disease and the majority of patients with osteoporosis do not receive any treatment [110]. However, this is no longer true since there are many treatments available for osteoporosis that could be considered as standard care. Decision-makers are more interested in comparisons between active drugs to determine first-line options. As there is a lack of trial data directly comparing the effectiveness of different treatments, indirect comparison is required to assess cost-effectiveness between active comparators.

Cost-effectiveness analyses between active comparators have started to appear in the osteoporosis literature, for example, for denosumab [98, 111], strontium ranelate [112] and zoledronic acid [113]. Indirect comparisons of efficacy between drugs are less robust because of different baseline characteristics of the populations studied and overlapping confidence intervals for the effect of treatment [114]. Such analyses should therefore be interpreted with great caution.

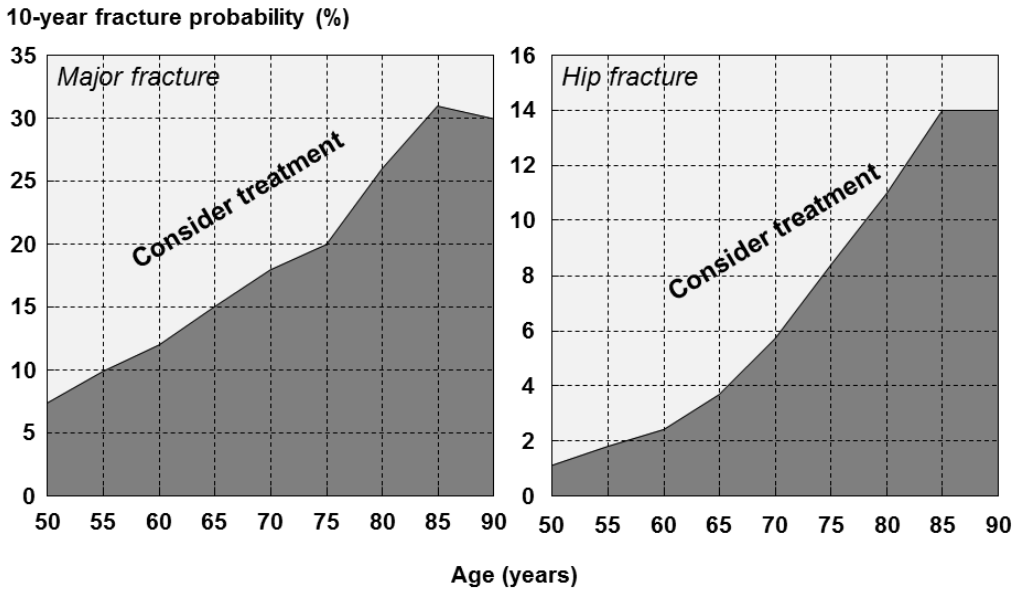
*COST-EFFECTIVE INTERVENTION THRESHOLDS*

Recent developments in fracture risk assessment, such as the use of the FRAX algorithm, have led to new applications in health economics of osteoporosis. First, there is a growing body of literature on the interaction between FRAX and treatment efficacy suggesting that for some agents (for example, bazedoxifene, clodronate, denosumab), there is a significant interaction between fracture probability and efficacy [115]. This has a significant impact on summary estimates of efficacy, and hence on cost-effectiveness.

Secondly, FRAX enables the estimation of risk based on a wider range of clinical risk factors and evaluation of treatment efficacy in populations at differing levels of risk [116]. The cost-effectiveness of drug treatments can therefore be estimated in various types of patients with different combinations of clinical risk factors. FRAX can therefore help identify new high-risk populations (i.e. patients with different combinations of clinical risk factors) that could benefit from cost-effective treatment.

Finally, economic evaluations are also increasingly being used to determine cost-effective intervention thresholds in order to guide clinical guidelines. Thus, health economic evaluations have been conducted in several countries to determine at what levels of fracture risk treatment should be initiated [80, 81, 117, 118]. In the UK, the intervention threshold at the age of 50 years corresponds to a 10-year probability of a major osteoporotic fracture of 7.5% [117]. This increases progressively with age to 30% at the age of 80 years. In Switzerland, use of a fixed FRAX-based intervention threshold of 15% for both women and men would permit cost-effective treatment [80]. In Belgium, a "translational approach" was used to define intervention thresholds by examining 10-year fracture probabilities equivalent to those currently accepted for reimbursement of treatment in Belgium (Figure 3) [119]. This approach will, however, need to be supported by health economic analyses [119]. Many country-dependent factors could have an impact on intervention thresholds, including fracture cost, intervention cost, and willingness-to-pay [81]. Intervention thresholds should therefore be determined on a per-country basis.

Figure 3| *Intervention thresholds in Belgium [119].*

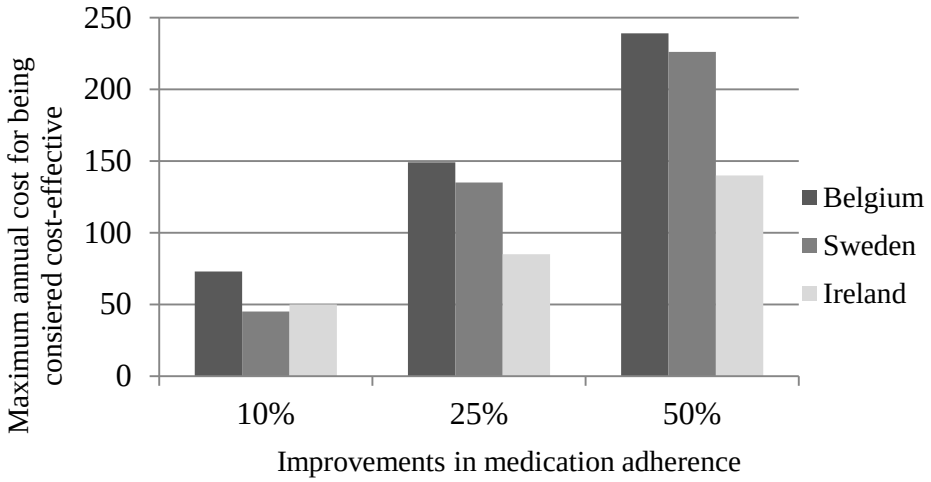



*ECONOMIC VALUE OF IMPROVING ADHERENCE*

Consideration of new therapeutic options and behavioural interventions that improve medication adherence is currently leading to questions regarding their impact on clinical and economic outcomes. Several studies have assessed the effects of improvements in adherence on fracture outcomes [120-123]. Other studies have estimated the potential economic value (in terms of cost per QALY gained) of interventions that improve medication adherence [36, 37, 64, 124]. Currently, no studies have examined the cost-effectiveness of a specific adherence-enhancing intervention. The economic value of improving adherence was assessed using a variety of hypothetical interventions, which differ according to cost (e.g., marginal or one-time cost) and improvements in adherence (between 10% and 50%).

The results of these studies suggest that interventions that improve adherence are likely to confer cost-effective benefits [36, 37, 64, 124]. Therefore, in the USA, a hypothetical intervention with a one-time cost of $250 that reduced discontinuation by 30% was reported to have an ICER of $29 571 per QALY gained [124]. In studies conducted in Belgium [36], Sweden [37], and Ireland [64], it has been estimated that an intervention that improves adherence by 10% is cost-effective at a maximum yearly cost of between €45 and €70 (Figure 4). For a hypothetical intervention that improves adherence by 50%, it is cost-effective to spend between €140 and €239 per year. The economic value of improving adherence could be situation-specific and improve with the increasing baseline risk for fractures [64, 124].

**Figure 4|** *Maximum yearly cost (in €) for an adherence-enhancing intervention to be considered cost-effective. Data from [36, 37, 64].*




*For Sweden, improvement in medication adherence at 25% should be read at 30%. In Ireland, a longer refill gap period (9-weeks) was selected to define persistence resulting in higher base-case adherence levels.*

This work has required methods of incorporating medication adherence into the models. As medication non-adherence affects both costs and outcomes, it could have a substantial impact on the cost-effectiveness of management strategies in osteoporosis and should be incorporated in pharmacoeconomic analyses [64, 122, 125]. In particular, when comparing drugs with different adherence profiles, the lack of inclusion of these concepts could bias the results and lead to suboptimal allocation of resources [126]. Integrating medication adherence into economic analyses in osteoporosis is a complex and difficult task, and has been extensively discussed elsewhere [74, 126].

## DISCUSSION

An increasing number of epidemiological and economic studies have revealed the immense burden of osteoporotic fractures, and this is expected to increase further in the future. Information from these studies will help establish priorities between interventions and diseases and guide research priorities. Furthermore, economic analyses have suggested that recent advances in the prevention and treatment of osteoporosis, including novel treatments, fracture risk assessment, and improved medication adherence, are an appropriate and efficient way of allocating healthcare resources. Such analyses may also contribute to a more efficient healthcare system.

HTA is a rapidly evolving discipline. As more countries use HTA to inform healthcare decisions, the harmonization of HTA between jurisdictions has been discussed in order to avoid duplication of effort [127]. Clinical data for new technologies usually apply across countries, but cost-effectiveness (and therefore appraisals of technologies for reimbursement) should be evaluated at a

national level because differences in the incidence of the disease, the availability of health resources, clinical practice patterns, and relative prices may impact on cost-effectiveness [128]. The development of key principles [129] and good practice, as well as international collaboration between experts, could facilitate a common process for the conduct of HTA for resource-allocation decisions.

There are currently major developments in the methods for economic evaluation in osteoporosis:

- Incorporation of medication adherence into pharmacoeconomic analyses in osteoporosis [74, 126].
- Use of FRAX in health economics of osteoporosis [116].
- Use of microsimulation models, which are beginning to supplant cohort models in HTA [130].
- In the absence of randomized controlled trials directly comparing active comparators, use of indirect treatment comparisons and network meta-analysis may provide useful evidence for selecting the best option [131].
- Characterization of uncertainty.

Alternative approaches to the assessment of QALY have also been developed, including discrete-choice experiment (DCE) [132, 133] and contingent valuation. DCEs have been increasingly used to elicit collective preferences of subgroups of patients in healthcare [134]. DCE is an attribute-based survey approach for measuring value, in which patient preference is determined by the levels of different attributes [135]. DCEs help determine important attributes and provide input on what patients with a particular disease prefer and/or are willing to pay.

Despite the growth of HTA over the past decades, its overall impact on policy-making may be limited [14]. The role of science is however to inform, not to dictate policy decisions. Humphreys and Piot recently argued that scientific evidence alone is not a sufficient basis for health policy and that other factors (such as democratic and human rights considerations) should be taken into consideration in health policy [136].

In summary, HTA helps decision-makers efficiently allocate healthcare resources. In the field of osteoporosis, HTA reports have revealed a considerable burden of fracture and the economic value of the prevention of fracture and the treatment of osteoporosis.

## ACKNOWLEDGEMENT

This paper is based on an expert consensus meeting held by the Belgian Bone Club under the auspices of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

## REFERENCES


1. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633-50.
2. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. Osteoporos Int. 2004;15(2):108-12.
3. Hiligsmann M, Bruyere O, Ethgen O, Gathon HJ, Reginster JY. Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women. Bone. 2008;43(6):991-4.
4. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int. 2000;11(8):669-74.
5. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012.
6. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: implications for risk assessment. J Bone Miner Res. 2002;17(7):1237-44.
7. Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. Nat Rev Rheumatol. 2010;6(2):99-105.
8. Ström O, Borgström F, Kanis J, Compston J, Cooper A, McCloskey E, et al. Osteoporosis: Burden, health care provision and opportunities in the European Union. Arch Osteoporos. 2011;6:59-155.
9. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2008;19(4):399-428.
10. International Network of Agencies of Health Technology Assessment INAHTA Health Technology Assessment glossary. http://www.inahta.org/HTA/Glossary/#_Health_Technology_Assessment. 2012. Cited 1 April 2012.
11. Jonsson E, Banta D. Management of health technologies: an international view. BMJ. 1999;319(7220):1293-U42.
12. Banta D, Jonsson E. History of HTA: Introduction. Int J Technol Assess Health Care. 2009;25 Suppl 1:1-6.
13. Martelli F, La Torre G, Di Ghionno E, Staniscia T, Neroni M, Cicchetti A, et al. Health technology assessment agencies: an international overview of organizational aspects. Int J Technol Assess Health Care. 2007;23(4):414-24.
14. Oliver A, Mossialos E, Robinson R. Health technology assessment and its influence on health-care priority setting. Int J Technol Assess Health Care. 2004;20(1):1-10.
15. Banta D, Oortwijn W. Health technology assessment and health care in the European Union. Int J Technol Assess Health Care. 2000;16(2):626-35.
16. Goodman C. HTA 101. Introduction to Health Technology Assessment. http://www.nlm.nih.gov/nichsr/hta101/hta101.pdf 2004. Cited 1 April 2012.
17. Melton LJ, 3rd, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis? J Bone Miner Res. 1992;7(9):1005-10.
18. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. Bone. 2001;29(6):517-22.
19. Dhanwal DK, Cooper C, Dennison EM. Geographic variation in osteoporotic hip fracture incidence: the growing importance of asian influences in coming decades. J Osteoporos. 2010:757102.

20. Johnell O, Borgstrom F, Jonsson B, Kanis J. Latitude, socioeconomic prosperity, mobile phones and hip fracture risk. Osteoporos Int. 2007;18(3):333-7.
21. Elffors I, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker J, et al. The variable incidence of hip fracture in southern Europe: the MEDOS Study. Osteoporos Int. 1994;4(5):253-63.
22. Roy DK, Pye SR, Lunt M, O'Neill TW, Todd C, Raspe H, et al. Falls explain between-center differences in the incidence of limb fracture across Europe. Bone. 2002;31(6):712-7.
23. Langley J, Samaranayaka A, Davie G, Campbell AJ. Age, cohort and period effects on hip fracture incidence: analysis and predictions from New Zealand data 1974-2007. Osteoporos Int. 2011;22(1):105-11.
24. Martyn CN, Cooper C. Prediction of burden of hip fracture. Lancet. 1999;353(9155):769-70.
25. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. Lancet. 2006;367(9504):36-43.
26. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. Osteoporos Int. 1992;2(6):285-9.
27. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. JAMA. 2009;302(14):1573-9.
28. Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, et al. Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporos Int. 2011;22(5):1277-88.
29. Melton LJ, 3rd, Kearns AE, Atkinson EJ, Bolander ME, Achenbach SJ, Huddleston JM, et al. Secular trends in hip fracture incidence and recurrence. Osteoporos Int. 2009;20(5):687-94.
30. Hiligsmann M, Bruyere O, Roberfroid D, Dubois C, Parmentier Y, Carton J, et al. Trends in hip fracture incidence and in the prescription of anti-osteoporosis medications during same time period in Belgium (2000-2007). Arthritis Care Res (Hoboken). 2012;64(5):744-50
31. Reginster JY, Gillet P, Gosset C. Secular increase in the incidence of hip fractures in Belgium between 1984 and 1996: need for a concerted public health strategy. Bull World Health Organ. 2001;79(10):942-6.
32. Abrahamsen B, Vestergaard P. Declining incidence of hip fractures and the extent of use of anti-osteoporotic therapy in Denmark 1997-2006. Osteoporos Int. 2010;21(3):373-80.
33. Melton LJ, 3rd, Kanis JA, Johnell O. Potential impact of osteoporosis treatment on hip fracture trends. J Bone Miner Res. 2005;20(6):895-7.
34. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet. 2011;377(9773):1276-87.
35. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385-97.
36. Hiligsmann M, Rabenda V, Bruyere O, Reginster JY. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy. 2010;96(2):170-7.
37. Landfeldt E, Lundkvist J, Strom O. The societal burden of poor persistence to treatment of osteoporosis in Sweden. Bone. 2011;48(2):380-8.
38. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res. 2008;23(12):1923-34.

39. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.
40. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis. 2006;65(5):654-61.
41. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab. 2005;90(5):2816-22.
42. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22.
43. Cooper C, Reginster JY, Cortet B, Diaz-Curiel M, Lorenc RS, Kanis JA, et al. Long-term treatment of osteoporosis in postmenopausal women: a review from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF). Curr Med Res Opin. 2012;28(3):475-91.
44. Mazziotti G, Bilezikian J, Canalis E, Cocchi D, Giustina A. New understanding and treatments for osteoporosis. Endocrine. 2012;41(1):58-69.
45. Devogelaer JP, Goemaere S, Boonen S, Body JJ, Kaufman JM, Reginster JY, et al. Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus document of the Belgian Bone Club. Osteoporos Int. 2006;17(1):8-19.
46. Body JJ, Bergmann P, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. Osteoporos Int. 2010;21(10):1657-80.
47. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312(7041):1254-9.
48. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int. 2007;18(8):1033-46.
49. Ensrud KE, Lui LY, Taylor BC, Schousboe JT, Donaldson MG, Fink HA, et al. A comparison of prediction models for fractures in older women: is more better? Arch Intern Med. 2009;169(22):2087-94.
50. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ. 2009;339:b4229.
51. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int. 2007;18(8):1109-17.
52. Kanis JA, Oden A, Johansson H, McCloskey E. Pitfalls in the external validation of FRAX. Osteoporos Int. 2012;23(2):423-31.
53. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, et al. Interpretation and use of FRAX in clinical practice. Osteoporos Int. 2011;22(9):2395-411.
54. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Spine-hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporos Int. 2011;22(3):839-47.

55. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int. 2011;22(3):809-16.
56. Gehlbach S, Saag KG, Adachi JD, Hooven FH, Flahive J, Boonen S, et al. Previous fractures at multiple sites increase the risk for subsequent fractures: The global longitudinal study of osteoporosis in women. J Bone Miner Res. 2012;27(3):645-53.
57. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1999;14(5):821-8.
58. Kayan K, Johansson H, Oden A, Vasireddy S, Pande K, Orgee J, et al. Can fall risk be incorporated into fracture risk assessment algorithms: a pilot study of responsiveness to clodronate. Osteoporos Int. 2009;20(12):2055-61.
59. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006;38(6):922-8.
60. Rabenda V, Mertens R, Fabri V, Vanoverloop J, Sumkay F, Vannecke C, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int. 2008;19(6):811-8.
61. Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int. 2006;17(11):1645-52.
62. Rabenda V, Reginster JY. Overcoming problems with adherence to osteoporosis medication. Expert Rev Pharmacoecon Outcomes Res. 2010;10(6):677-89.
63. Ross S, Samuels E, Gairy K, Iqbal S, Badamgarav E, Siris E. A meta-analysis of osteoporotic fracture risk with medication nonadherence. Value Health. 2011;14(4):571-81.
64. Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. Value Health. 2012;15(5):604-12.
65. Gleeson T, Iversen MD, Avorn J, Brookhart AM, Katz JN, Losina E, et al. Interventions to improve adherence and persistence with osteoporosis medications: a systematic literature review. Osteoporos Int. 2009;20(12):2127-34.
66. Hiligsmann M, Salas M, Hughes DA, Manias E, Gwadry-Sridhar F, Linck P, et al. Most Effective Patient Compliance Interventions with Osteoporosis Medications. ISPOR 16th Annual International Meeting Abstracts, Baltimore, MD, 21-25 May 2011. Value Health 14:A130.
67. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int. 2012;23(1):317-26.
68. Montori VM, Shah ND, Pencille LJ, Branda ME, Van Houten HK, Swiglo BA, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. Am J Med. 2011;124(6):549-56.
69. Nielsen D, Ryg J, Nielsen W, Knold B, Nissen N, Brixen K. Patient education in groups increases knowledge of osteoporosis and adherence to treatment: a two-year randomized controlled trial. Patient Educ Couns. 2010;81(2):155-60.
70. Drummond M, Sculpher M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes, 3rd edition. Oxford University Press, New-York 2007.

71. Taylor RS, Drummond MF, Salkeld G, Sullivan SD. Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. BMJ. 2004;329(7472):972-5.
72. Drummond M, Jonsson B, Rutten F. The role of economic evaluation in the pricing and reimbursement of medicines. Health Policy. 1997;40(3):199-215.
73. Cleemput I, van Wilder P, Huybrechts M, Vrijens F. Belgian methodological guidelines for pharmacoeconomic evaluations: toward standardization of drug reimbursement requests. Value Health. 2009;12:441-49.
74. Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. Osteoporos Int. 2011;22(10):2565-73.
75. Palmer S, Byford S, Raftery J. Economics notes: types of economic evaluation. BMJ. 1999;318(7194):1349.
76. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis--a review of the literature and a reference model. Osteoporos Int. 2007;18(1):9-23.
77. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation, 2nd edn. Oxford University Press: New-York 2007.
78. Raftery J. NICE: faster access to modern treatments? Analysis of guidance on health technologies. BMJ. 2001;323(7324):1300-3.
79. World Health Organization. Macroeconomics and Health: Investing in Health for Economic Development. Report of the Commission onMacroeconomics and Health. http://whqlibdoc.who.int/publications/2001/924154550x.pdf. 2011. Cited 10 April 2012.
80. Lippuner K, Johansson H, Borgstrom F, Kanis JA, Rizzoli R. Cost-effective intervention thresholds against osteoporotic fractures based on FRAX(R) in Switzerland. Osteoporos Int. 2012;23(11):2579-2589.
81. Borgstrom F, Johnell O, Kanis JA, Jonsson B, Rehnberg C. At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. Osteoporos Int. 2006;17(10):1459-71.
82. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care. Health Technology Assessment (HTA). KCE Reports 100B (D/2008/10.273/95). Belgian Health Care Knowledge Centre, Brussels. 2008.
83. George B, Harris A, Mitchell A. Cost-effectiveness analysis and the consistency of decision making: evidence from pharmaceutical reimbursement in Australia (1991 to 1996). Pharmacoeconomics. 2001;19(11):1103-9.
84. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ. 2004;13(5):437-52.
85. National institute for Health and Clinical Excellence. Appraising life-extending, end of life treatments. Available under: http://www.nice.org.uk/media/88A/F2/SupplementaryAdviceTACEoL.pdf. 2012. Cited 10 April 2012.
86. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. BMJ. 2011;342:d1548.
87. Petrou S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. BMJ. 2011;342:d1766.

88. O'Brien B. Economic evaluation of pharmaceuticals. Frankenstein's monster or vampire of trials? Med Care. 1996;34(12 Suppl):DS99-108.
89. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ. 2006;15(7):677-87.
90. Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? Pharmacoeconomics. 2000;17(5):445-59.
91. Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, et al. Modelling in economic evaluation: an unavoidable fact of life. Health Econ. 1997;6(3):217-27.
92. Sheldon TA. Problems of using modelling in the economic evaluation of health care. Health Econ. 1996;5(1):1-11.
93. Kassirer JP, Angell M. The journal's policy on cost-effectiveness analyses. N Engl J Med. 1994;331(10):669-70.
94. National Institute for Health and Clinical Excellence. Final appraisal determination. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. http://www.nice.org.uk/nicemedia/live/11704/51970/51970.pdf 2010
95. Kanis J, McCloskey E, Jonsson B, Cooper A, Ström O, Borgström F. An evaluation of the NICE guidance for the prevention of osteoporotic fragility fractures in postmenopausal women. Arch Osteoporos. 2012;5:19-48.
96. Fleurence RL, Spackman DE, Hollenbeak C. Does the funding source influence the results in economic evaluations? A case study in bisphosphonates for the treatment of osteoporosis. Pharmacoeconomics. 2010;28(4):295-306.
97. Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment. Decision analytic modelling in the economic evaluation of health technologies. A consensus statement. Pharmacoeconomics. 2000;17(5):443-4.
98. Hiligsmann M, Reginster JY. Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. Pharmacoeconomics. 2011;29(10):895-911.
99. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. Health Econ. 2004;13(5):405-15.
100. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993;13(4):322-38.
101. Hiligsmann M, Ethgen O, Bruyere O, Richy F, Gathon HJ, Reginster JY. Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. Value Health. 2009;12(5):687-96.
102. Muller D, Pulm J, Gandjour A. Cost-effectiveness of different strategies for selecting and treating individuals at increased risk of osteoporosis or osteopenia: a systematic review. Value Health. 2012;15(2):284-98.
103. Zethraeus N, Ben Sedrine W, Caulin F, Corcaud S, Gathon HJ, Haim M, et al. Models for assessing the cost-effectiveness of the treatment and prevention of osteoporosis. Osteoporos Int. 2002;13(11):841-57.
104. Hiligsmann M, Reginster JY. Health economics in osteoporosis. Temas (topics) de osteoporosis y otras enfermedades oseas 2012. p. 337-58.

105. Fleurence RL, Iglesias CP, Johnson JM. The cost effectiveness of bisphosphonates for the prevention and treatment of osteoporosis: a structured review of the literature. Pharmacoeconomics. 2007;25(11):913-33.
106. Fleurence RL, Iglesias CP, Torgerson DJ. Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. Osteoporos Int. 2006;17(1):29-40.
107. Schousboe JT. Cost effectiveness of screen-and-treat strategies for low bone mineral density: how do we screen, who do we screen and who do we treat? Appl Health Econ Health Policy. 2008;6(1):1-18.
108. Hiligsmann M, Bruyere O, Reginster JY. Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women. Osteoporos Int. 2010;21(1):157-65.
109. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. Bone. 2010;47(1):34-40.
110. Borgstrom F, Kanis JA. Health economics of osteoporosis. Best Pract Res Clin Endocrinol Metab. 2008;22(5):885-900.
111. Jonsson B, Strom O, Eisman JA, Papaioannou A, Siris ES, Tosteson A, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. Osteoporos Int. 2011;22(3):967-82.
112. Hiligsmann M, Bruyere O, Reginster JY. Cost-effectiveness of strontium ranelate versus risedronate in the treatment of postmenopausal osteoporotic women aged over 75 years. Bone. 2010;46(2):440-6.
113. Akehurst R, Brereton N, Ariely R, Lusa T, Groot M, Foss P, et al. The cost effectiveness of zoledronic acid 5 mg for the management of postmenopausal osteoporosis in women with prior fractures: evidence from Finland, Norway and the Netherlands. J Med Econ. 2011;14(1):53-64.
114. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev. 2002;23(4):570-8.
115. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD. FRAX((R)) with and without bone mineral density. Calcif Tissue Int. 2012;90(1):1-13.
116. Strom O, Borgstrom F, Kleman M, McCloskey E, Oden A, Johansson H, et al. FRAX and its applications in health economics--cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example. Bone. 2010;47(2):430-7.
117. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. Case finding for the management of osteoporosis with FRAX--assessment and intervention thresholds for the UK. Osteoporos Int. 2008;19(10):1395-408.
118. Tosteson AN, Melton LJ, 3rd, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, et al. Cost-effective osteoporosis treatment thresholds: the United States perspective. Osteoporos Int. 2008;19(4):437-47.
119. Johansson H, Kanis JA, McCloskey EV, Oden A, Devogelaer JP, Kaufman JM, et al. A FRAX(R) model for the assessment of fracture probability in Belgium. Osteoporos Int. 2011;22(2):453-61.
120. Danese MD, Badamgarav E, Bauer DC. Effect of adherence on lifetime fractures in osteoporotic women treated with daily and weekly bisphosphonates. J Bone Miner Res. 2009;24(11):1819-26.
121. Cotte FE, Cortet B, Lafuma A, Avouac B, Hasnaoui AE, Fardellone P, et al. A model of the public health impact of improved treatment persistence in post-menopausal osteoporosis in France. Joint Bone Spine. 2008;75(2):201-8.

122. Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY. Potential clinical and economic impact of nonadherence with osteoporosis medications. Calcif Tissue Int. 2010;86(3):202-10.
123. Rietbrock S, Olson M, van Staa TP. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. QJM. 2009;102(1):35-42.
124. Patrick AR, Schousboe JT, Losina E, Solomon DH. The economics of improving medication adherence in osteoporosis: validation and application of a simulation model. J Clin Endocrinol Metab. 2011;96(9):2762-70.
125. Strom O, Borgstrom F, Kanis JA, Jonsson B. Incorporating adherence into health economic modelling of osteoporosis. Osteoporos Int. 2009;20(1):23-34.
126. Hiligsmann M, Boonen A, Rabenda V, Reginster JY. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. Expert Rev Pharmacoecon Outcomes Res. 2012;12(2):159-66.
127. Hutton J, Trueman P, Facey K. Harmonization of evidence requirements for health technology assessment in reimbursement decision making. Int J Technol Assess Health Care. 2008;24(4):511-7.
128. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009;12(4):409-18.
129. Drummond MF, Schwartz JS, Jonsson B, Luce BR, Neumann PJ, Siebert U, et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care. 2008;24(3):244-58; discussion 362-8.
130. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics. 2006;24(11):1043-53.
131. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health. 2011;14(4):429-37.
132. Darba J, Restovic G, Kaskens L, Balbona MA, Carbonell A, Cavero P, et al. Patient preferences for osteoporosis in Spain: a discrete choice experiment. Osteoporos Int. 2011;22(6):1947-54.
133. de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Pols HA, Koes BW, Steyerberg EW. Patients' preferences for osteoporosis drug treatment: a discrete choice experiment. Osteoporos Int. 2008;19(7):1029-37.
134. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics. 2008;26(8):661-77.
135. Ryan M. Discrete choice experiments in health care. BMJ. 2004;328(7436):360-1.
136. Humphreys K, Piot P. Scientific evidence alone is not sufficient basis for health policy. BMJ. 2012;344:e1316.

# PART 1

## ECONOMIC EVALUATION

CHAPTER 3

# COST-EFFECTIVENESS OF DENOSUMAB IN THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROTIC WOMEN

**Hiligsmann M**, Ben Sedrine W, Boonen A, Dirksen CD, Reginster JY

*Expert Review of Pharmacoeconomics & Outcomes research, 2013, 13(1), 19-28*

## ABSTRACT

Denosumab is a novel biological agent for the treatment of osteoporosis in postmenopausal women with increased risk of fractures. With limited health care resources, economic evaluations are increasingly being used by decision-makers to optimize health care resource allocation. The cost-effectiveness of denosumab has been evaluated in various studies and a systematic literature research was conducted up to April 2012 to identify all published research articles and research abstracts presented at various congresses. This article provides a systematic review of 4 articles and 8 abstracts reporting on cost-effectiveness of denosumab in the treatment of osteoporosis. In most economic evaluations, denosumab has been considered as a cost-effective treatment compared with first-line and second-line options (including generic alendronate) in the treatment of women with high risk of fractures.

## KEYWORDS

Cost-effectiveness, denosumab, osteoporosis.

## INTRODUCTION

Osteoporosis is an increasingly major public health problem around the world. It is estimated that, in western countries, one in three women and one in five men over the age of 50 years will experience an osteoporotic fracture during their remaining lifetime [1]. Osteoporotic fractures result in significant morbidity, excess mortality and reduction in quality of life [2-4]. They also impose a financial burden on health-care systems. In six major European countries, the burden of osteoporotic fractures was estimated in 2010 at €31 billion [5].

Oral bisphosphonates have been the most widely prescribed drugs for the treatment and prevention of osteoporosis, with demonstrated efficacy in reducing the risks of vertebral and non-vertebral fractures [6]. However, effectiveness in real-life settings is jeopardized by poor adherence. Several studies have reported that between 50% and 75% of women who initiate oral bisphosphonates are non-adherent within one year [7, 8], and that the majority of patients with hip fractures did not receive any medication [9-11]. Poor adherence reduces the effectiveness of osteoporosis treatment, increasing fracture rates [12]. Approximately 50% of the potential clinical benefits of oral bisphosphonates are expected to be lost due to non-adherence and, thus, reduces the cost-effectiveness of osteoporosis medications [13-15].

Denosumab is a novel agent for the treatment of osteoporosis in postmenopausal women with increased risk of fractures. In a 3-year randomized clinical trial including postmenopausal women with osteoporosis, subcutaneous injection of denosumab every 6 months significantly reduced the risk of hip, vertebral and non-vertebral fractures [16]. An attractive feature of the 6-monthly regimen with denosumab is that adherence may be improved compared with weekly regimens, thereby improving effectiveness in real-life settings and preventing more fractures [17]. Recently, a 2-year randomized open label study indeed demonstrated significantly greater treatment adherence and persistence for subcutaneous injection of denosumab every 6 months compared with oral alendronate once weekly [18, 19]. Risks ratio for denosumab compared with alendronate at 12 months were estimated at 0.58 for non-adherence ($p = 0.043$) and 0.54 for non-persistence ($p = 0.049$) [19].

With introduction of new (and more expensive) treatments, the economic value of newer agents compared with existing alternatives needs to be assessed. Health economic evaluations have become increasingly important to support priority setting in health care and help decision makers to efficiently allocate healthcare resources. It is therefore not surprising that studies on the cost-effectiveness of denosumab have been recently performed. Understanding the different aspects of the evidence of cost-effectiveness of denosumab would be very useful for health care decision-making and also to identify gaps in the current evidence that could inform future economic evaluations. This study was therefore designed to systematically review and critically appraise

existing economic evaluations of denosumab for the treatment of postmenopausal osteoporotic women.

## METHODS

### *SEARCH STRATEGY*

A systematic literature search was conducted to find all published research articles as well as all research abstracts presented in various congresses. The literature search was conducted using various databases: Medline, Centre for Reviews and Dissemination databases, Cost-effectiveness Analysis Registry and the Cochrane Library for articles up to April, 30$^{th}$ 2012. In addition, congress abstracts were searched directly from four congress organizers: the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the European Congress for Clinical and Economic Aspects of Osteoporosis (ECCEO), the International Osteoporosis Foundation (IOF), and the American Society for Bone and Mineral Research (ASBMR). Abstracts presented at the ISPOR Annual International Meeting in June 2012 were also searched. For the ISPOR abstracts, the related congress posters were searched on the congress web site.

The following search terms were used: denosumab AND (cost-effectiveness or cost-utility or economic or evaluation or cost) for research articles and the term 'denosumab' was used to find congress abstracts. Evaluation reports from the manufacturer or from different national agencies were not searched. Nevertheless, formal Health Technology Assessment (HTA) reports are covered by the searched HTA database and these were not excluded if found in the database search. Editorials or comments were excluded. The search was also restricted to English-language literature.

### *SELECTION OF STUDIES*

We included full economic evaluation of denosumab (in one of the treatment arms) for the treatment of postmenopausal women with osteoporosis. A full economic evaluation was defined as the comparison of costs and outcomes, including cost-effectiveness analyses (CEAs) in which results are usually expressed as a cost per unit of effect (e.g. cost per fracture prevented gained), and cost-utility analyses (CUAs) in which results are generally expressed as a cost per quality-adjusted life year (QALY) gained [20]. Two reviewers (MH and WBS) independently applied these criteria to identify citations during title and abstract screening. Reference lists of identified economic evaluation were also manually searched. Congress abstracts that were published as full articles were excluded as well as duplicate abstracts reporting the same data.

*Data extraction and critical appraisal*

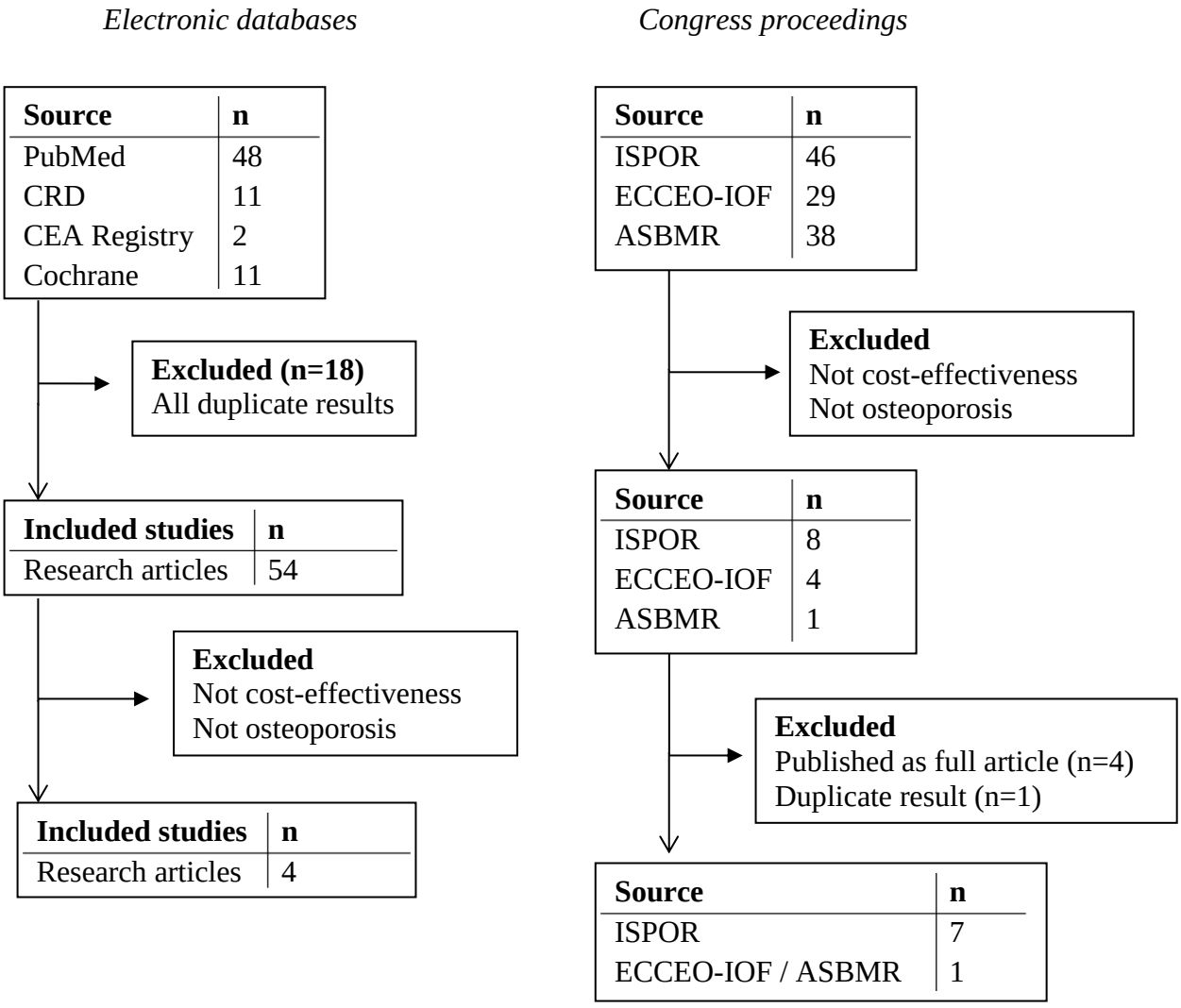
Data were extracted using a standard collection form. We extracted study characteristics from articles related to: 1) study design (country, perspective, outcome measure, model type, time horizon, price year, discount rates, funding), 2) population, comparator and treatments characteristics (efficacy source, adherence, treatment duration, offset time, drug cost) and 3) study outcomes (results, sensitivity analyses). Reported incremental cost-effectiveness ratios (ICER) were presented in Euros, British pounds or US dollars, no other adjustments were made. A simple extraction form was used to extract information for congress abstracts including congress name, year/month, country, perspective, model, population, comparator, ICER and funding. Two reviewers (MH and WBS) independently extracted data from articles and congress abstracts.

Quality of selected articles were appraised with the British Medical Journal (BMJ) checklist [21] by two independent reviewers (AB and CD), not being authors of any of the original articles. Thirty-five items related to study design, data collection, analysis and interpretation of results were scored using "Yes", "No", "Not Clear", "Substandard", and "Not Applicable". Discrepancies in rating were resolved by consensus and a third reviewer (MH) was consulted to reconcile disagreements. The methodological quality of the congress abstracts was not evaluated.

## RESULTS

The initial database search identified 72 research articles and 113 congress abstracts; of which 18 articles were excluded as duplicates (Figure 1). We reviewed all titles and abstracts of these articles and subsequently excluded 50 research articles and 105 congress abstracts that did not meet our inclusion criteria. Four abstracts were excluded because they were published as full articles [22-25] and one abstract was a duplicate result [26]. A total of four research articles [17, 27-29] and eight congress abstracts [30-37] fulfilled our inclusion criteria. Among the published articles, three of these were 'original research' [17, 27, 28] (funded by the manufacturer of denosumab, Amgen) and the last one provided a description of a dossier submitted by Amgen in UK and the subsequent NICE appraisal [29, 38].

**Figure 1**| *Literature search flow chart (electronic databases and congress proceedings)*



*SELECTED ARTICLES*

Two studies were conducted in Belgium [27, 28], one in Sweden [17] and one in UK [29] (Table 1). Economic perspectives included societal (n=1) [17] and health care payer (n=3) [27-29]. All studies used a lifetime time horizon and were Markov models with quality-adjusted life-years (QALY) as the outcome measure. Markov models were analyzed using a cohort-based approach [17, 29] or an individual patient simulation [27, 28]. Discount rates varied between studies and were based on local guidelines for economic evaluations. Three studies were funded by the manufacturer of denosumab [17, 27, 28] and the last one was a review of the manufacturer submission to the National Institute of Clinical Excellence (NICE) in UK and the NICE appraisal funded by a UK Health Technology Assessment program [29].

Efficacy data from the FREEDOM Trial [16] that was published in 2009 was used in all studies. Treatment duration in modeling was assumed for a maximum of 3 [27, 28] or 5 [17, 29] years although all models used a lifetime horizon to capture the long-term effects of preventing fractures. Adherence to denosumab was included in the base-case in only two studies [17, 28]. For the main comparators, Hiligsmann et al. [28] incorporated both compliance and persistence, while Jonsson et al. [17] only included medication persistence. Treatment duration was assumed to linearly decline to zero after stopping therapy, for a maximum of 1-year [27-29] or over the same period as the time on treatment [17]. Two studies used the same assumption for denosumab and the comparators [17, 29] while the effect of denosumab after stopping therapy was conservatively assumed to be shorter compared with the alternatives in another study [28]. None of the studies included side-effects for denosumab as the clinical trial reported no significant differences in the total incidence of adverse events and serious adverse events between subjects who received denosumab and those who received placebo [16]. In addition to drug cost (estimated at €415 [27, 28], €425 [17] and £366 [29] per year), all studies incorporated the cost of two yearly visits to general physicians (GPs) in the base-case. However, the Evidence Review of Group (ERG) commissioned by the NICE expressed concerns about this assumption, suggesting that denosumab might be flagged for administration and monitoring in secondary care only [29]. Nevertheless, assuming one dose of denosumab administrated per year in secondary care had a limited impact on the cost-effectiveness of denosumab [29].

Out of the four articles, fourteen comparisons between denosumab and alternative treatment were performed. Comparator treatments included no treatment (n=3), generic alendronate (n=2), branded alendronate (n=1), ibandronate (n=1), raloxifene (n=1), risedronate (n=2), strontium ranelate (n=2), teriparatide (n=1) and zoledronic acid (n=1).

**Table 1**| *Characteristics of published articles assessing the cost-effectiveness of denosumab in the treatment of osteoporosis*

| First author | Country | Perspective | Outcome measure | Model type | Time horizon | Price year | Discount rates (cost, QALY) | Funding |
|---|---|---|---|---|---|---|---|---|
| Hiligsmann et al., 2010 [27] | Belgium | Health-care payer | QALYs | Markov: microsimulation | Lifetime | € 2009 | 3% - 1.5% | Amgen |
| Hiligsmann et al., 2011 [28] | Belgium | Health-care payer | QALYs | Markov: microsimulation | Lifetime | € 2009 | 3% - 1.5% | Amgen |
| Jonsson et al., 2011 [17] | Sweden | Societal | QALYs | Markov: cohort | Lifetime | € 2008 | 3% - 3% | Amgen |
| Scotland et al., 2011 [29] | UK | UK health and social care perspective | QALYs | Markov: cohort | Lifetime | £ 2009 | 3.5% - 3.5% | NIHR HTA - Amgen |

*QALY Quality-adjusted life-year*

Results of the cost-effectiveness literature of denosumab are reported on Table 2. Overall, the ICER of denosumab falls below commonly accepted thresholds for cost-effectiveness. Although, in most countries, there are no generally accepted or recommended thresholds for cost-effectiveness, interventions with cost per QALY gained lower than €30,000-€60,000 were usually considered as 'good value for money' in treating osteoporosis [39, 40]. Using a Belgian healthcare payer perspective, denosumab was deemed to be cost-effective compared with no treatment in patients with similar characteristics to those included in the FREEDOM Trial and in a population of patients that would be eligible to receive treatment in many European countries based on osteoporosis medication reimbursement guidelines, i.e. with BMD T-score ≤-2.5 or prevalent vertebral fracture [27]. The same authors further assessed the cost-effectiveness of denosumab compared with the most relevant alternatives (i.e. branded and generic oral bisphosphonates) [28]. The analysis demonstrated that denosumab was cost-effective compared with oral bisphosphonates (including generic alendronate) in the treatment of postmenopausal women with osteoporosis aged over 60 years, assuming a willingness to pay of €40,000 per QALY gained. A sensitivity analysis suggested that results were influenced by adherence to oral bisphosphonates and fracture risk. In a Swedish setting using a societal perspective, denosumab was also shown to be cost-effective compared with generic alendronate, risedronate and strontium ranelate for typical Swedish women receiving osteoporosis medications [17]. In the UK, the cost-effectiveness of denosumab was demonstrated compared with no treatment, strontium ranelate, raloxifene, intravenous ibandronate and teriparatide [29]. The cost-effectiveness of denosumab versus zoledronic acid, which was considered by the ERG as the main comparator, is however uncertain, and is sensitive to the assumptions associated with the costs of administration of denosumab (i.e. two GPs visits per year or one dose of denosumab per year in secondary care). The ERG founded it difficult to separate denosumab and zoledronic acid on grounds of cost-effectiveness in UK [29]. Table 3 presents the appraisal of the original studies on the cost-effectiveness of denosumab (except the NICE appraisal [29]) using the BMJ criteria. Published articles are based on good-quality models that have been previously validated [41, 42]. Study design was generally clearly described. Studies did however not describe quantities of resource use separately from their unit costs, likely because in models no original costing studies were done but costs related to these events were derived from other sources. All studies reported incremental analyses and major outcomes were presented in a disaggregated and aggregated form. Only two studies reported stochastic data and performed probabilistic sensitivity analyses [27, 28], while the choice of variables for sensitivity analyses and the range over which they are varied were not fully reported.

**Table 2**| *Results of published articles assessing the cost-effectiveness of denosumab in the treatment of osteoporosis*

| Article | Population | Comparator | Results (ICER of denosumab vs comparator treatment) |
|---|---|---|---|
| Hiligsmann et al., 2010 [27] | FREEDOM Trial* | No treatment | €28,441 |
| | Women with BMD T-score ≤-2.5 and no prior fracture | No treatment | €25,061 (60 y), €8948 (70 y), €-642 (80 y) |
| Hiligsmann et al., 2011 [28] | Women aged 70 years with BMD T-score ≤-2.5 and no prior fracture | Generic alendronate<br>Branded alendronate<br>Branded risedronate | €22,220<br>€14,120<br>€-209 |
| | Women aged 70 years with prevalent vertebral fracture | Generic alendronate<br>Branded alendronate<br>Branded risedronate | €14,166<br>€19,718<br>€4456 |
| Jonsson et al., 2011 [17] | Typical Swedish patient population** | Generic alendronate<br>Risedronate<br>Strontium ranelate<br>No treatment | €27,090<br>€11,545<br>€5015<br>€14,458 |
| Scotland et al., 2011 [29] | Women aged 70 years with a T-score of -2.5 or less and no prior fracture | Strontium ranelate<br>Raloxifene<br>No treatment<br>Zoledronic acid (ZoL)<br>Intravenous ibandronate<br>Teriparatide (PTH) | Dominant<br>£9289<br>£29,223<br>ICER of Zol***: £70,900<br>Dominant<br>ICER of PTH***: £772,424 |
| | Women aged 70 years with a T-score of -2.5 or less with a prior fragility fracture | Strontium ranelate<br>Raloxifene<br>No treatment<br>Zoledronic acid (ZoL)<br>Intravenous ibandronate<br>Teriparatide (PTH) | Dominant<br>£2000<br>£12,381<br>ICER of ZoL***: £29,029<br>Dominant<br>ICER of PTH***: £451,269 |

*ICER Incremental cost-effectiveness ration (expressed in cost per QALY gained), Y years.*

** Women aged 72 years, T-score of -2.2 and 23.6% of those had prevalent vertebral fracture*
*** Women aged 71 years, T-score≤-2.5 and a prevalence of morphometric vertebral fractures of 34%*
**** Incremental cost-effectiveness ratio of zoledronic acid or of teriparatide compared with denosumab*

**Table 3**| *Results of quality appraisal of articles assessing the cost-effectiveness of denosumab: BMJ criteria*

| | Hiligsmann et al. 2010 [27] | Hiligsmann et al. 2011[28] | Jonsson et al. 2011 [17] |
|---|---|---|---|
| **Study Design** | | | |
| 1 The research question is stated. | Yes | Yes | Yes |
| 2 The economic importance of the research question is stated. | Sub | Yes | Yes |
| 3 The viewpoint(s) of the analysis is (are) clearly stated and justified. | Yes | Yes | Yes |
| 4 The rationale for choosing alternative programmes or interventions compared is stated. | Yes | Yes | Yes |
| 5 The alternatives being compared are clearly described. | Yes | Yes | Yes |
| 6 The form of the economic evaluation used is stated. | Yes | Yes | Yes |
| 7 The choice of form of economic evaluation is justified in relation to the questions addressed. | Yes | Yes | No |
| **Data Collection** | | | |
| 8 The source(s) of effectiveness estimates used is (are) stated. | Yes | Yes | Yes |
| 9 Details of the design and results of effectiveness study are given (if based on a single study). | NA | NA | NA |
| 10 Details of the methods of synthesis or meta-analysis of estimates are given | NA | NA | NA |
| 11 The primary outcome measures(s) for the economic evaluation are clearly stated. | Yes | Yes | Yes |
| 12 Methods to value benefits are stated. | Sub | Sub | Yes |
| 13 Details of the subjects from whom valuations were obtained were given. | Sub | Yes | Yes |
| 14 Productivity changes (if included) are reported separately. | NA | NA | No |
| 15 The relevance of productivity changes to the study question is discussed. | No | No | No |
| 16 Quantities of resource use are reported separately from their unit costs. | Sub | Sub | Sub |
| 17 Methods for the estimation of quantities and unit costs are described. | No | Sub | No |
| 18 Currency and price data are recorded. | Yes | Yes | Yes |
| 19 Details of currency of price adjustments for inflation or currency conversion are given. | Yes | Yes | Yes |
| 20 Details of any model used are given. | Yes | Yes | Yes |
| 21 The choice of model used and the key parameters on which it is based are justified. | Yes | Yes | Yes |

| | | | |
|---|---|---|---|
| **Analysis and Interpretation of Results** | | | |
| 22 Time horizon of costs and benefits is stated. | Yes | Yes | Yes |
| 23 The discount rate(s) is (are) justified. | Yes | Yes | Yes |
| 24 The choice of discount rate(s) is (are) justified. | Yes | Yes | Yes |
| 25 An explanation is given if costs and benefits are not discounted. | NA | NA | NA |
| 26 Details of statistical tests and confidence intervals are given for stochastic data. | Yes | Yes | No |
| 27 The approach to sensitivity analysis is given. | Yes | Yes | Sub |
| 28 The choice of variables for sensitivity analysis is justified. | Sub | Sub | No |
| 29 The ranges over which the variables are varied are justified. | Sub | Sub | No |
| 30 Relevant alternatives are compared. | Sub | Sub | Sub |
| 31 Incremental analysis is reported. | Yes | Yes | Yes |
| 32 Major outcomes are presented in a disaggregated as well as aggregated form. | Yes | Yes | Yes |
| 33 The answer to the study question is given. | Yes | Yes | Yes |
| 34 Conclusions follow from the data reported. | Yes | Yes | Yes |
| 35 Conclusions are accompanied by the appropriate caveats. | Yes | Yes | Yes |

*NA Not Applicable, NC  Not Clear, Sub  Substandard*

*SELECTED ABSTRACTS*

Most of the included congress abstracts (7 out of 8) were presented at different ISPOR meetings between 2009 and 2012. One study was presented at the ECCEO-IOF meeting. From the 7 included ISPOR abstracts, the related congress posters were available in 4 cases [31, 32, 35, 37]. Five abstracts were funded by the manufacturer of denosumab and three did not provide information about funding sources.

Characteristics and results from these abstracts are reported in Table 4. Research was conducted by 8 different authors in 6 different countries. Abstracts during 2009-2011 provided further evidence on the cost-effectiveness of denosumab in other European settings, suggesting that denosumab is also cost-effective compared with current treatment options in Greece, Portugal, Scotland, Spain and UK [30, 31, 35-37].

Recently, three abstracts reported the cost-effectiveness of denosumab in the Unites States at the ISPOR Annual International Meeting in June 2012, with contrasting results. Based on a previously validated model, Parthan et al. showed that denosumab represented a good value for money compared to branded bisphosphonates in the overall postmenopausal population and was either cost-effective or dominant compared with generic alendronate in the higher-risk subgroups [32]. Jiang et al. also compared denosumab and generic alendronate in US using a new type of model and concluded that denosumab was not cost-effective [33]. Finally, Beaubran et al. suggested that denosumab was not cost-effective compared with raloxifene [34]. Unfortunately, posters were not available for these two last congress abstracts and limited information was available on the new model structure and the efficacy data used in the abstract, making it difficult to assess the quality of these evaluations.

**Table 4**| *Characteristics and results of congress abstracts assessing the cost-effectiveness of denosumab in the treatment of osteoporosis*

| Year (month) | Congress | First author | Country | Perspective | Population | Comparators | ICER of denosumab vs comparator | Funding |
|---|---|---|---|---|---|---|---|---|
| 2009 (09) | ASBMR and IOF-ECCEO | Ström | UK | Health care payer | Women aged 70 years with BMD T-score of -2.5 | Risedronate<br>Placebo | £14,300<br>£10,700 | Amgen |
| 2011 (05) | ISPOR | Cristino | Portugal | National health service | NR | Alendronate-colecalciferol | €14,487 | NR |
| 2011 (11) | ISPOR | Davies | Scotland | National health service | Women aged 70 years with BMD T-score of -2.5 (and no prior fracture) | Strontium ranelate<br>Ibandronate<br>Raloxifene<br>No treatment<br>Zoledronate (ZoL) | Dominant<br>Dominant<br>£4,339<br>£22,380<br>ICER of ZoL = £120,000 | Amgen |
| 2011 (11) | ISPOR | Darba | Spain | National healthcare system | Women aged 65years with BMD T-score of -2.5 and a prevalence of morphometric vertebral fractures of 36% | No treatment<br>Generic alendronate<br>Generic risedronate<br>Ibandronate<br>Strontium ranelate | €17,345<br>€15,397<br>€14,543<br>Dominant<br>Dominant | Amgen |
| 2011 (11) | ISPOR | Athanasakis | Greece | Third party payer | FREEDOM TRial | No treatment<br>Alendronate<br>Ibandronate<br>Risedronate<br>Strontium ranelate | €18,813<br>€24,784<br>€13,727<br>€18,436<br>€11,114 | Amgen |
| 2012 (06) | ISPOR | Parthan | USA | Third party payer | High risk subgroups (Overall PMO population) | Risedronate<br>Ibandronate<br>Generic alendronate | Dominant (NR)<br>Dominant (Dominant)<br>$28,200 ($103,000) | Amgen |
| 2012 (06) | ISPOR | Jiang | USA | Societal | Not clear | Generic alendronate | $2,111,647 | NR |
| 2012 (06) | ISPOR | Beaubran | USA | Managed care | Women aged over 65 years with BMD T-score ≤ -2.5 | Raloxifene | Dominated | NR |

*BMD Bone mineral density, ICER Incremental cost-effectiveness ratio, NR Not reported, PMO Postmenopausal osteoporosis*

## EXPERT COMMENTARY

Denosumab represents a new therapeutic option for the treatment of postmenopausal women at high risk of fractures. The cost-effectiveness of denosumab in this indication has been assessed against multiple treatments in several studies. In these analyses, denosumab has been considered to be cost-effective compared with most treatment options (including oral treatments). The cost-effectiveness of densoumab versus once yearly injection of zoledronic acid remains however uncertain, depending mainly on assumptions about the costs of administration of denosumab.

This review identified 4 published articles based on good-quality models and 8 additional congress abstracts that estimated the cost-effectiveness of denosumab in the treatment of postmenopausal osteoporotic women. Published articles were only conducted in three European countries (Belgium, Sweden and UK). Congress abstracts suggest that denosumab is likely to be cost-effective in other European countries with similar characteristics. The transferability of economic evaluations across jurisdictions could however be uncertain as differences in the incidence of disease, the availability of health resources, clinical practice patterns, and relative prices may impact cost-effectiveness [43]. Recently, research abstracts about the cost-effectiveness of denosumab in US were presented at the ISPOR congress (2012) and we could therefore expect full articles in non-European countries in the near future.

Other gaps were identified. First, adherence and persistence with osteoporosis medications were not incorporated in all studies, despite their potential impact on the cost-effectiveness results [13, 44]. In particular, when comparing drugs with potential differences in adherence and persistence (e.g. denosumab versus oral drug treatment), the lack of inclusion of these concepts could bias the results and lead to suboptimal allocation of resources [13]. Recently published data on adherence and persistence to denosumab compared with alendronate would definitely be interesting for further cost-effectiveness analyses of denosumab [18, 19]. There are also some investigations of denosumab in particularly high risk patients, suggesting a better cost-effectiveness profile of this drug in this particular clinical condition [45, 46].

Second, no direct comparisons between denosumab and other treatments are currently available. Indirect comparisons of efficacy between drugs are less robust because of different baseline characteristics of the populations studied and overlapping confidence intervals for the effect of treatment [47]. Further research would therefore be required to confirm the findings, ideally with head-to-head observational studies of denosumab compared with oral bisphosphonates, to provide more robust data. Further studies are also required to evaluate adverse events and long-term safety of denosumab in real-world clinical practice that could potentially be included in further cost-effectiveness analyses.

Further investigation is also needed to assess the effect of denosumab after stopping therapy. Recent data suggest that the treatment benefit achieved (changes in BMD) with 2 years of denosumab therapy was reversed within 2 years of treatment discontinuation, and remained above those of the group previously treated with placebo [48]. There is however no consensus on this effect, including potential differences with other osteoporotic treatments. Another issue is the monitoring costs of denosumab. Existing economic evaluations incorporated the cost of two yearly visits to general physicians, but the ERG in the UK expressed concerns about this assumption, suggesting that denosumab might be flagged for administration and monitoring in secondary care only. Finally, assessing the value of perfect information would be useful to inform policy decisions about future research in this topic [49].

We followed recommendations for conducting reviews of economic evaluations [50]. Two independent reviewers were used for literature search, data extraction and quality assessment. Critical appraisal of published articles was done by two authors that were not authors of the original articles, using the BMJ checklist, as recommended [50]. Some discrepancies were observed between reviewers, but were only a matter of interpretation. The critical appraisal of congress abstracts is not meaningful as too little information is included in congress abstracts which must therefore be interpreted with the greatest caution.

Most studies included in these review were funded by the manufacturer of denosumab: three published articles out of the four and five of the eight congress abstracts. However, as reported in a case study in bisphosphonates, the funding source did not seem to significantly affect the reporting of low or high incremental cost-effectiveness ratios in the treatment of osteoporosis [51]. In addition, models used in funding studies were previously validated and have been used to assess the cost-effectiveness of other osteoporosis medications [41, 42].

## FIVE-YEAR VIEW

Poor adherence to therapy represents a major problem in the treatment of osteoporosis. Improving medication adherence is becoming urgently needed and the use of longer dosing regimen could be an effective way to enhance medication adherence. Administered as a subcutaneous injection every six months, denosumab is a novel attractive drug for the treatment of osteoporosis. Denosumab also represents a cost-effective alternative compared with existing oral osteoporosis treatments, and may be considered as a first-line treatment option for patients at high risk of fracture. As a future standard of treatment, it is likely that there will be a number of cost-effectiveness articles of denosumab in the future. In particular, one would expect cost-effectiveness articles of denosumab in non-European countries, as well as using real-world adherence and effectiveness data.

## KEY ISSUES

- Denosumab is a novel agent for the treatment of osteoporosis in postmenopausal women with demonstrating efficacy in reducing the risk of hip, vertebral and non-vertebral fractures.
- The cost-effectiveness of denosumab in the treatment of postmenopausal women with osteoporosis has been evaluated in various published research articles and abstracts presented at various congresses.
- In most economic evaluations, denosumab has been deemed to be cost-effective compared with first-line and second-line drug therapies in the treatment of postmenopausal women with high risk of fractures.
- Further articles on the cost-effectiveness analyses of denosumab are expected in non-European countries and using real-world adherence and effectiveness data.

## REFERENCES


1. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012; 23(9):2239-56
2. Haentjens P, Magaziner J, Colon-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med. 2010;152(6):380-90.
3. Lips P, van Schoor NM. Quality of life in patients with osteoporosis. Osteoporos Int. 2005;16(5):447-55.
4. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15(1):38-42.
5. Ström O, Borgström F, Kanis J, Compston J, Cooper A, McCloskey E, et al. Osteoporosis: Burden, health care provision and opportunities in the European Union. Archives of Osteoporosis. 2011;6:59-155.
6. Reginster JY. Treatment of postmenopausal osteoporosis. Brit Med J. 2005;330(7496):859-60.
7. Rabenda V, Hiligsmann M, Reginster JY. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. Expert Opin Pharmacother. 2009;10(14):2303-15.
8. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med. 2009;122(2 Suppl):S3-13.
9. Carnevale V, Nieddu L, Romagnoli E, Bona E, Piemonte S, Scillitani A, et al. Osteoporosis intervention in ambulatory patients with previous hip fracture: a multicentric, nationwide Italian survey. Osteoporos Int. 2006;17(3):478-83.
10. Liel Y, Castel H, Bonneh DY. Impact of subsidizing effective anti-osteoporosis drugs on compliance with management guidelines in patients following low-impact fractures. Osteoporos Int. 2003;14(6):490-5.
11. Rabenda V, Vanoverloop J, Fabri V, Mertens R, Sumkay F, Vannecke C, et al. Low incidence of anti-osteoporosis treatment after hip fracture. J Bone Joint Surg Am. 2008;90(10):2142-8.
12. Curtis JR, Yun H, Lange JL, Matthews R, Sharma P, Saag KG, et al. Does medication adherence itself confer fracture protection? an investigation of the healthy adherer effect in observational data. Arthritis Care Res (Hoboken). 2012;64(12):1855-63.
13. Hiligsmann M, Boonen A, Rabenda V, Reginster JY. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. Expert Rev Pharmacoecon Outcomes Res. 2012;12(2):159-66.
14. Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. Value Health. 2012; 15(5):604-12
15. Hiligsmann M, Rabenda V, Bruyere O, Reginster JY. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy. 2010;96(2):170-7.
16. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.

17. Jonsson B, Strom O, Eisman JA, Papaioannou A, Siris ES, Tosteson A, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. Osteoporos Int. 2011;22(3):967-82.
18. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int. 2012;23(1):317-26.
19. Kendler DL, McClung MR, Freemantle N, Lillestol M, Moffett AH, Borenstein J, et al. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. Osteoporos Int. 2011;22(6):1725-35.
20. Drummond M, Sculpher M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes, 3th edition. New-York: Oxford University Press; 2007.
21. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.
22. Hiligsmann M, Reginster J. Cost-effectiveness of denosumab compared with generic alendronate in the treatment of postmenopausal osteoporotic women. Value Health. 2010;13:A309-A10.
23. Hiligsmann M, Reginster J. Cost-effectiveness of denosumab compared with generic alendronate in the treatment of postmenopausal osteoporotic women. Osteoporosis Int 2011;22:S112.
24. Hiligsmann M, Reginster J. Cost-effectiveness of denosumab compared with oral bisphosphonates in the treatment of postmenopausal osteoporotic women. Osteoporosis Int 2010;21:S30.
25. Hiligsmann M, Reginster J. Cost-utility of denosumab for the treatment of postmenopausal osteoporotic women 20. 2009:S16.
26. Ström O, Macarios D, Badamgarav E, Borgstrom F, Tosteson A, Kanis J. A UK Denosumab Cost-Effectiveness Model Incorporating FRAX and Adherence. J Bone Miner Res. 2009;24:S141.
27. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. Bone. 2010;47(1):34-40.
28. Hiligsmann M, Reginster JY. Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. Pharmacoeconomics. 2011;29(10):895-911.
29. Scotland G, Waugh N, Royle P, McNamee P, Henderson R, Hollick R. Denosumab for the prevention of osteoporotic fractures in post-menopausal women: a NICE single technology appraisal. Pharmacoeconomics. 2011;29(11):951-61.
30. Ström O, Macarios D, Badamgarav E, Borgstrom F, Jonsson B, Tosteson A, et al. Cost-effectiveness model for denosumab incorporating FRAX and adherence in a UK Setting. Osteoporosis Int 2009;20:S20.
31. Davies A, Compston J, Ferguson S, McCloskey E, Shearer A, Taylor A. Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Scotland. Value Health. 2011;14:A310.
32. Parthan A, Deflin M, Yurgin N, Huang J, Taylor D. Cost-effectiveness of denosumab versus oral bisphosphonates in the Unites States for post-menopausal osteoporosis. Value Health. 2012;15:A38.
33. Jiang Y, Hay J. The cost-effectiveness of denosumab for the prevention of osteoporotic fractures in the setting of the Unites States. Value Health. 2012;15:A38.
34. Beaubrun A, Daugherty J. Cost-utility analysis of denosumab versus raloxifene for treating osteoporosis in post-menopausal women in the United States. Value Health. 2012;14:A129.

35. Darba J, Kaskens L, Sorio F. Cost-utility of denosumab for the treatment of postmenopausal osteoporosis in Spain. Value Health. 2011;14:A311.
36. Cristino J, Canhão H, Perelman J, Santos C, Pereira J. Cost-utility analysis of denosumab versus standrad care in the treatment of post-menopausal osteoporosis in Portugal. Value Health. 2011;14:A128.
37. Athanasakis K, Karampli E, Hollandezos M, Papagiannopoulou V, Badamgarav E, Intorcia M, et al. A cost-effectiveness analysis of denosumab for the treatment of post-menopausal osteoporosis in Greece. Value Health. 2011;14:A138.
38. Waugh N, Royle P, Scotland G, Henderson R, Hollick R, McNamee P. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Health Technol Assess. 2011;15 Suppl 1:51-9.
39. Strom O, Borgstrom F, Sen SS, Boonen S, Haentjens P, Johnell O, et al. Cost-effectiveness of alendronate in the treatment of postmenopausal women in 9 European countries--an economic evaluation based on the fracture intervention trial. Osteoporos Int. 2007;18(8):1047-61.
40. Tosteson AN, Melton LJ, 3rd, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, et al. Cost-effective osteoporosis treatment thresholds: the United States perspective. Osteoporos Int. 2008;19(4):437-47.
41. Hiligsmann M, Ethgen O, Bruyere O, Richy F, Gathon HJ, Reginster JY. Development and Validation of a Markov Microsimulation Model for the Economic Evaluation of Treatments in Osteoporosis. Value in Health. 2009;12(5):687-96.
42. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis - a review of the literature and a reference model. Osteoporosis International. 2007;18(1):9-23.
43. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009;12(4):409-18.
44. Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. Osteoporos Int. 2011;22(10):2565-73.
45. McClung M, Boonen S, Torring O, Roux C, Rizzoli R, Bone H, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. J Bone Miner Res. 2011;27(1):211-18..
46. Bouee S, Lafuma A, Fagnani F, Meunier PJ, Reginster JY. Estimation of direct unit costs associated with non-vertebral osteoporotic fractures in five European countries. Rheumatol Int. 2006;26(12):1063-72.
47. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev. 2002;23(4):570-8.
48. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab. 2011;96(4):972-80.
49. Fenwick E, Claxton K, Sculpher M. The value of implementation and the value of information: combined and uneven development. Med Dec Making. 2008;28:21-32.
50. Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. JAMA. 2002;287(21):2809-12.

51. Fleurence RL, Spackman DE, Hollenbeak C. Does the funding source influence the results in economic evaluations? A case study in bisphosphonates for the treatment of osteoporosis. Pharmacoeconomics. 2010;28(4):295-306.

# CHAPTER 4

## A SYSTEMATIC REVIEW OF COST-EFFECTIVENESS ANALYSES OF DRUGS FOR POSTMENOPAUSAL OSTEOPOROSIS

**Hiligsmann M**, Evers SM, Ben Sedrine W, Kanis JA, Ramaekers B, Reginster JY, Silverman S, Wyers CE, Boonen A

*PharmacoEconomics [Epub Ahead of Print]*

## ABSTRACT

*BACKGROUND*: Given the limited availability of healthcare resources and the recent introduction of new anti-osteoporosis drugs, the interest in cost-effectiveness of drugs in postmenopausal osteoporosis remains and even increases.

*OBJECTIVE*: This study aims to identify all recent economic evaluations on drugs for postmenopausal osteoporosis, to critically appraise the reporting quality and to summarize the results.

*METHODS*: A literature search using Medline, the National Health Service Economic Evaluation database and the Cost-Effectiveness Analysis Registry was undertaken to identify original articles published between January 1, 2008 and December 31, 2013. Studies that assessed cost-effectiveness of drugs in postmenopausal osteoporosis were included. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used to assess the quality of reporting of these articles.

*RESULTS*: Of 1,794 articles identified, 39 studies fulfilled the inclusion criteria. They were conducted in 14 different countries and 9 active interventions were assessed. When compared with no treatment, active osteoporotic drugs were generally cost-effective in postmenopausal women aged over 60-65 years with low bone mass, especially those with prior vertebral fractures. Key drivers of cost-effectiveness included individual fracture risk, medication adherence, selected comparators and country-specific analyses. Quality of reporting varied between studies with an average score of 17.9 out of 24 (range from 7 to 21.5).

*CONCLUSION*: This review found a substantial number of published cost-effectiveness analyses of drugs in osteoporosis in the last six years. Results and critical appraisal of these articles can help decision makers when prioritizing health interventions and can inform the development of future economic evaluations.

## INTRODUCTION

Osteoporosis represents a major public health problem, especially in the Western world. It is estimated that 27.5 million of people have osteoporosis in the 27 countries of the European Union [1]. In 2010, approximately 3.5 million new fractures occurred in these countries and the economic impact of these fractures was estimated to be nearly €37 billion and accounted for 1,180,000 quality-adjusted life years lost [1]. In the Unites States, osteoporosis is responsible for more than 2 million fractures every year, and these are associated with costs estimated to be US$19 billion in 2005, rising to US$25.3 billion by 2025 [2].

Considering the limited availability of healthcare resources alongside major recent innovations in the management of osteoporosis, health technology assessment is increasingly important to help decision makers to efficiently allocate healthcare resources [3]. In 2007, two systematic reviews [4, 5] were published suggesting that oral bisphosphonates are cost-effective for the prevention and treatment of osteoporosis in women aged over 70 years, particularly in patients with risk factors for fracture. Over recent years, new treatment strategies have become available to prevent and treat osteoporosis, including bazedoxifene, denosumab, ibandronate, strontium ranelate and zoledronic acid [6]. Evidence about the safety and efficacy of these drugs has been provided [6, 7] and consideration of the cost-effectiveness of these new interventions has been adressed [8, 9].

An overview of the recent literature of cost-effectiveness analyses of drugs in postmenopausal osteoporosis would thus be important to help decision makers when prioritizing health interventions, to identify gaps in the current evidence and to inform the development of future economic evaluations. We therefore undertook a systematic review of the literature to identify recent economic evaluations of drugs for postmenopausal osteoporosis. Using narrative summaries, the review also aimed to provide insight into key drivers of cost-effectiveness ratios. Because the interpretation of the results depends on the quality of conducting and reporting studies, the quality of reporting of these economic evaluations was appraised using the recently developed Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [10, 11].

## METHODS

### *LITERATURE SEARCH*

A literature search was conducted using Medline, the National Health Service Economic Evaluation database (NHS EED) and the Cost-Effectiveness Analysis (CEA) Registry. We restricted our analysis to articles published after 2008, January 1st, since prior articles were covered in prior reviews [4, 5]. Titles and abstracts were initially searched in Medline using the following search algorithm: ‘osteoporosis OR fracture AND cost-effectiveness OR cost-utility OR economic OR cost’ (between 1/01/2008 and 31/06/2013). The search words ‘osteoporosis’ and ‘fractures’ were

used in NHS EED database and the CEA Registry. The search was restricted to English-language literature. Reference lists of identified economic evaluations and reviews [12] were manually searched. A last update using the same methodology was performed in January 2014 including articles published between 1/07/2013 and 31/12/2013.

*SELECTION OF STUDIES*

In a first step, we included in this systematic review full economic evaluations for the treatment or prevention of osteoporosis that compared at least two alternatives in terms of costs and outcomes, including cost-effectiveness and cost-utility analyses. In the second step, we excluded review articles, economic evaluations in male populations and other specific populations (such as women with glucocorticoid-induced osteoporosis), studies about screening strategies and intervention thresholds (using hypothetical treatment) as well as evaluations that did not include a drug (by example model of care, lifestyle or nutritional intervention) or that focused on improving medication adherence. Three reviewers (MH, SS, CW) independently applied these criteria to identify articles during title and abstract screening. A consensus meeting was used to resolve discrepancies.

*DATA EXTRACTION AND QUALITY ASSESSMENT*

Data were extracted using a standardized extraction table. We extracted study characteristics related to publication (year, journal name), study design (country, perspective, outcome measure, model type, time horizon, discount rates and funding), population, comparators and results. Two reviewers (MH and WBS) extracted data of the articles. Incremental cost-effectiveness ratios were reported as in the articles and no adjustment for year or purchasing power parity was done. Some key-drivers of cost-effectiveness such as fracture risk and medication adherence were also identified and reported.

Studies were then appraised for quality of reporting using the CHEERS statement [10, 11]. This checklist was produced with the aim of harmonizing the presentation of information and thus raising the quality standard of economic evaluations and improving interpretation of systematic reviews of such analyses. At least two reviewers (MH, SE, WBS, BR, SS, CW and/or AB) independently appraised the studies. Twenty-four items addressed in six categories (title and abstract, introduction, methods, results, discussion and other) and were scored using 'Yes' (reported in full), 'Partially reported', 'No' (not reported), 'Not Applicable'. In order to estimate a score of reporting, we assigned a score of 1 if the fulfilled the requirement of reporting for that item completely, 0.5 for partial report and otherwise zero. Therefore, the maximum score for an article that reported completely all information was 24.

# RESULTS

*STUDY SELECTION PROCESS*

Figure 1 shows the flow chart for the identification of studies. The initial database search identified 1,794 articles, of which 117 were excluded as duplicates. After screening by title and abstract, 94 full economic evaluations were identified. Of those, only 42 remained after the second step. Studies were mainly excluded because they did not include a drug (n=15), or because they concerned screening and intervention thresholds (n=15) or the burden of the improvement of medication adherence (n=8). Other excluded articles concerned male populations (n=2), specific populations (n=4), nutrition (n=4) or were about surgery (n=4), methodological work (n=1) or an abstract (n=1). After reading the full-text of the remaining 42 articles, 6 articles were excluded because they were not original studies or were not written in English language, or concerned screening programs or methodological issues. Thirty-six studies were then identified between 2008, January 1st and 2013, June, 30th. Further three articles were identified after the update of the literature till 2013, December, 31st.

*OVERVIEW OF INCLUDED STUDIES*

The characteristics of included studies are reported in Table 1. Twenty four of the 39 studies were conducted in the period 2008-2010 and fifteen between 2011 and 2013. Articles were mainly published in osteoporosis journals such as Osteoporosis International (n=10) and Bone (n=7), but also in health economic journals such as Journal of Medical Economics (n=4), Value in Health (n=2), Pharmacoeconomics (n=1) or Applied Health Economics & Health Policy (n=1). Most studies were conducted in Europe (n=29) (and especially in United Kingdom (n=9), Belgium (n=8) and Sweden (n=8)), followed by the United States and Canada (n=9) and Japan (n=2). Five articles considered several countries in the analysis [13-17].

A societal perspective was used in 10 studies and all studies used quality-adjusted life-years (QALY) as outcome except the article of Fardellone et al. [18] that used fractures avoided as outcome. Model-based cost-effectiveness analyses were used in all studies. Twenty-eight articles used a Markov cohort model while 8 studies used a microsimulation Markov model (mainly the model developed by Hiligsmann et al.[19]) and one used a discrete-event simulation model [13]. Seven studies applied fixed time horizon such as 3, 5 or 10 years [20-22, 18, 15, 23, 24], while the remaining studies (n=32) considered a lifetime horizon. Seven studies were not funded by pharmaceutical companies [25, 22, 19, 26-28, 24] and two did not mention the source of funding [17, 29].

**Figure 1**| *Literature search flow chart*

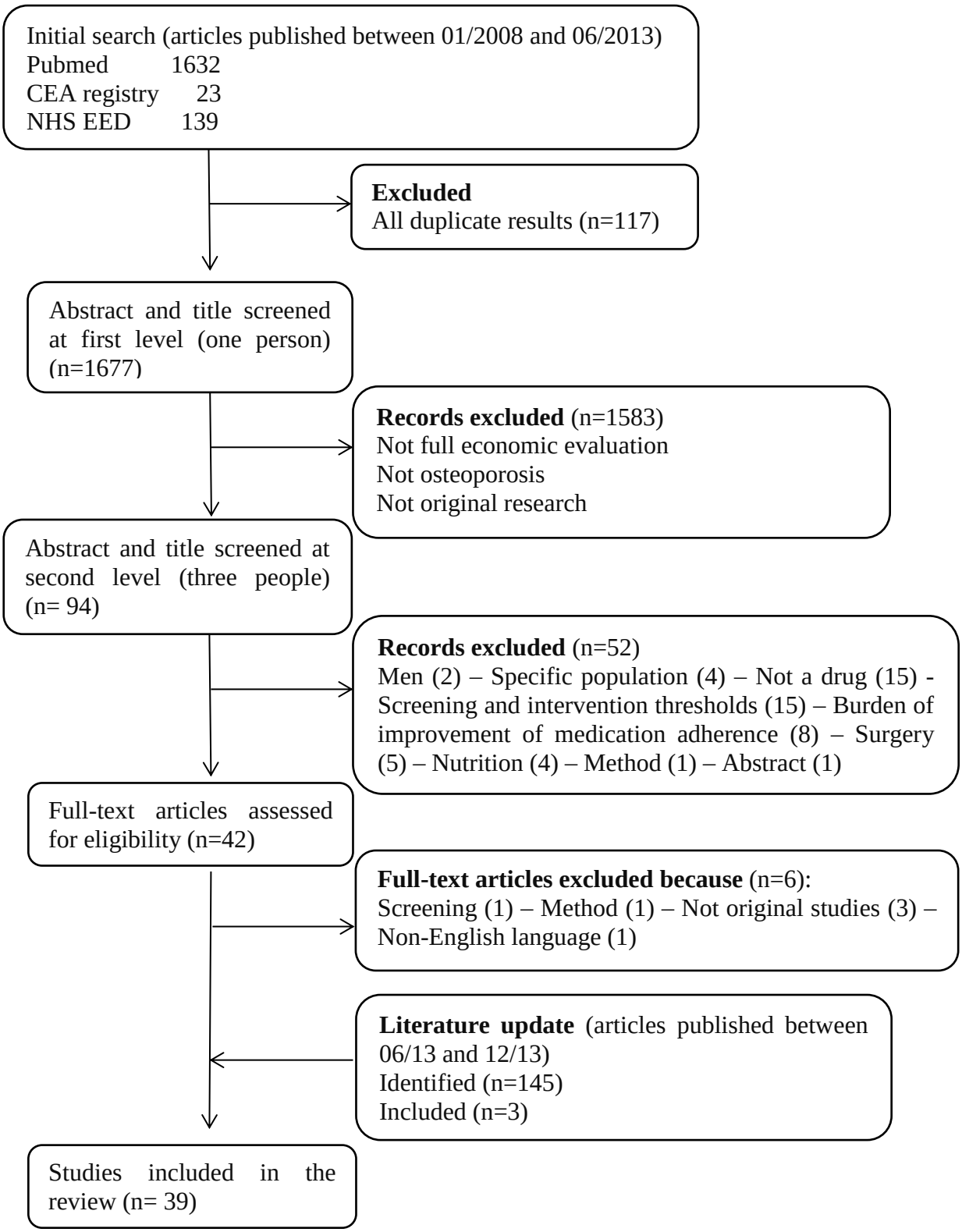


Table 2 presents characteristics of the studied population, the active intervention and comparator and the main results of the articles. Different study populations were investigated, including women with a low bone mass density based on the definition of the World Health Organization (bone mineral density (BMD) T-score of -2.5) [30], women with previous vertebral fractures, and populations similar to that of the clinical trials [31-34]. Fracture risk algorithms such as FRAX® that represents the 10-year probability of a major fracture and of hip fracture [35], were increasingly used to assess the cost-effectiveness of drugs among patients differing in specific combinations of clinical risk factors [36, 14, 37, 38, 26, 27, 39].

Nine active interventions were included in the studies, i.e. alendronate, bazedoxifene, denosumab, hormone therapy, ibandronate, raloxifene, risedronate, teriparatide and zoledronic acid. Generic alendronate was included in 9 studies [20, 40-43, 26, 27, 44, 39, 23] while no treatment was used as comparator in 22 of the 39 studies (56.4%). Eleven studies included at more than two active interventions in their analysis [13, 32, 18, 40, 45, 42, 15, 43, 44, 39, 24].

When compared with no treatment, active osteoporotic drugs (such as alendronate [19, 41, 15, 46, 26], bazedoxifene [14, 47], denosumab [33, 44, 39], raloxifene [38], risedronate [31, 48], strontium ranelate [36, 49], teriparatide [37, 50] and zoledronic acid [13]) were generally cost-effective, at commonly-accepted threshold for cost-effectiveness (about 45,000 € per QALY gained), in postmenopausal women aged over 60-65 years with low bone mass. In women with additional clinical risk factors such as prior fractures, active treatments could even be cost-effective from the age of 50 years [26]. Several drug therapies were also reported to be cost-saving in women aged over 80 years [49, 41, 26], meaning that the averted costs resulting from prevented fractures exceed the cost of the intervention.

Cost-effectiveness analyses among active comparators revealed that denosumab was cost-effective compared with many other osteoporotic agents including generic alendronate, especially in the high-risk subgroups [32, 42-44]. When using the subgroup analysis of women at higher risk of fractures, bazedoxifene was dominant compared with another selective estrogen receptor modulator (i.e. raloxifene) in three studies [21, 51, 16]. One study showed that strontium ranelate was cost-effective compared with risedronate [45] while two studies suggests that risedronate dominated generic alendronate [20, 23]. Zoledronic acid was shown to be cost-effective compared with branded bisphosphonates [13] and Murphy et al. [50] concluded that teriparatide was cost-effective compared with oral bisphosphonates in severe postmenopausal osteoporosis.

**Table 1**| *Characteristics of cost-effectiveness analyses of drugs for postmenopausal osteoporosis*

| Study (year) | Journal | Country | Perspective | Outcome measure | Model type | Time horizon | Discount rates | Industry funding |
|---|---|---|---|---|---|---|---|---|
| 1-Akehurst (2011) [13] | Journal of Medical Economics | Finland, Norway, Netherlands | Healthcare payer | QALY | Discrete-event individual-patient simulation model | Lifetime | Not reported | Novartis |
| 2-Alzahouri (2013) [25] | Joint Bone Spine | France | Healthcare system | QALY | Markov cohort model | Lifetime | 4%, 4% | No |
| 3-Berto (2010) [20] | Aging Clinical and Experimental Research | Italy | Healthcare system | QALY | Markov cohort model | 6 years | 3%, 3% | Sanofi-Aventis |
| 4-Borgstrom (2010) [36] | Osteoporosis International | UK | Healthcare payer | QALY | Markov cohort model | Lifetime | 3.5%, 3.5% | Servier |
| 5-Borgstrom (2010) [31] | Osteoporosis International | UK | Healthcare payer | QALY | Markov cohort model | Lifetime | 3.5%, 3.5% | Alliance for Better Bone Health |
| 6-Borgstrom (2011) [14] | Osteoporosis International | France, Germany, Italy, Spain, Sweden, UK | Healthcare payer | QALY | Markov cohort model | Lifetime | 3%, 3% for all countries except UK 3.5%, 3.5% | Wyeth |
| 7-Borgstrom (2010) [37] | Journal of Medical Economics | Sweden | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | Lilly Europe |
| 8-Chau (2012) [32] | Journal of Medical Economics | Canada | Public payer | QALY | Markov cohort model | Lifetime | 5%, 5% | Amgen |
| 9-Darbà (2013) [21] | Clinicoeconomics Outcomes Research | Spain | Healthcare payer | QALY | Markov cohort model | Until patients were 82 years of age | 3%, 3% | Pfizer |
| 10-Ding (2008) [22] | Journal of Bone and Mineral Metabolism | Japan | Healthcare payer | QALY | State transition model | 3 years | 5%, 5% | No |
| 11-Fardellone (2010) [18] | Joint Bone Spine | France | Healthcare payer | Fractures avoided | SImulation-based models | 3 years | Not reported | Novartis |
| 12-Grima (2008) [40] | Osteoporosis International | Canada | Healthcare payer | QALY | Markov cohort model | 5 years | 5%, 5% | Alliance for Better Bone Health |
| 13-Hiligsmann (2013) [51] | Journal of Bone & Mineral Research | Belgium | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 1.5% | Pfizer |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 14-Hiligsmann (2010) [45] | Bone | Belgium | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 1.5% | Servier |
| 15-Hiligsmann (2010) [49] | Osteoporosis International | Belgium | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 1.5% | Servier |
| 16-Hiligsmann (2009) [19] | Value in Health | Belgium | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 1.5% | No |
| 17-Hiligsmann (2010) [41] | Calcified Tissue International | Belgium | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 1.5% | Novartis |
| 18-Hiligsmann (2010) [33] | Bone | Belgium | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 1.5% | Amgen |
| 19-Hiligsmann (2011) [42] | Pharmacoeconomics | Belgium | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 1.5% | Amgen |
| 20-Ivergard (2010) [38] | Bone | US | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | Eli Lilly |
| 21-Jansen (2008) [15] | Current Medical Research & Opinion | UK, Netherlands | Healthcare payer | QALY | Markov model | 10 years | 4%, 4% (NL) – (3.5%, 3.5% UK) | Merck & Co |
| 22-Jonsson (2011) [43] | Osteoporosis International | Sweden | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | Amgen |
| 23-Kanis (2008) [26] | Bone | UK | Healthcare payer | QALY | Markov cohort model | Lifetime | 3.5%, 3.5% | No |
| 24-Kanis (2008) [27] | Osteoporosis International | UK | Healthcare payer | QALY | Markov cohort model | Lifetime | 3.5%, 3.5% | No |
| 25-Kim (2014) [16] | Osteoporosis International | Belgium, France, Germany, Ireland, Italy, Spain Sweden , UK | Healthcare payer | QALY | Markov cohort model | Lifetime | 3.0%, 3% for all countries, except for the UK (3.5%, 3.5%) and Ireland (4.0%, 4.0%) | Pfizer |
| 26-Lekander (2008) [17] | Bone | Sweden, UK, US | Societal | QALY | Markov cohort model | Lifetime | Not reported | NR |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 27-Lekander (2009) [67] | Journal of Women Health | US | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | Wyeth |
| 28-Lippuner (2012) [46] | Osteoporosis International | Switzerland | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | MSD |
| 29-Moriwaki (2013) [68] | Journal of Bone and Mineral Metabolism | Japan | Healthcare payer | QALY | Markov cohort model | Lifetime | 3%, 3% | Pfizer |
| 30-Murphy (2012) [50] | BMC Musculoskeletal Disorders | Sweden | Healthcare payer | QALY | Markov microsimulation model | Lifetime | 3%, 3% | Lilly |
| 31-Parthan (2013) [44] | Applied Health Economics & Health Policy | US | US third-party payer | QALY | Markov cohort model | Lifetime | 3%, 3% | Amgen |
| 32-Pham (2011) [28] | Journal of American Geriatrics Society | US | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | No |
| 33-Salpeter (2009) [29] | American Journal of Medicine | US | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | NR |
| 34-Seeman (2010) [34] | Bone | Sweden | Societal | QALY | Markov cohort model | Lifetime | 3.5%, 3.5% | Servier |
| 35-Strom (2010) [47] | Bone | Sweden | Societal | QALY | Markov cohort model | Lifetime | 3%, 3% | Pfizer |
| 36-Strom (2013) [39] | Osteoporosis International | UK | Healthcare payer | QALY | Markov cohort model | Lifetime | 3.5%, 3.5% | Amgen |
| 37-Thompson (2010) [23] | Value in Health | Germany | Healthcare payer | QALY | Markov cohort model | 5 years | 3%, 3% | Alliance for Better Bone Health |
| 38-Tosteson (2008) [24] | The American Journal of Managed Care | US | Healthcare payer | QALY | Markov cohort model | 10 years | 3%, 3% | No |
| 39-Wasserfallen (2008) [48] | Journal of Medical Economics | Switzerland | Healthcare payer | QALY | Markov cohort model | Lifetime | 3%, 3% | Sanofi-Aventis |

*NR Not Reported, QALY Quality-Adjusted Life-Years*

**Table 2**| *Results of cost-effectiveness analyses of drugs for postmenopausal osteoporosis*

| Study (year) | Population | Comparators | Results | |
|---|---|---|---|---|
| 1-Akehurst (2011) [13] | Postmenopausal women aged 50-80 years who have experienced one previous fracture and have a T-score of -2.5 | 2006 Finland, 2007 Netherlands | Zoledronic vs calcium/vitamin D, bisphosphonates | The ICER compared with calcium/vitamin D ranged from being cost-saving in all age groups in Norway, to €19,000 in Finland and €22,300 in Netherlands. Compared with the other branded bisphosphonates, zoledronic acid was cost-saving in many scenarios. Zoledronic acid may also be cost-effective compared with generic alendronate |
| 2-Alzahouri (2013) [25] | Postmenopausal 70-year-old woman with a T-score of -2.5 | 2011 | Branded alendronate vs no treatment | ICER compared to no treatment ranged from € 104,183 to € 413,473 per QALY when FRAX decreased from 10 to 3% |
| 3-Berto (2010) [20] | Postmenopausal women aged ≥ 65 years with a previous vertebral fracture | NR | Risedronate vs generic alendronate | ICER ranged from €36,099 (age 65-69) to cost-saving (from age 75-79) |
| 4-Borgstrom (2010) [36] | Postmenopausal women aged over 50 years using FRAX | 2006 | Strontium ranelate vs no treatment | At a threshold of £30,000 per QALY, strontium ranelate was generally cost-effective in women from an age of 65 years with prior fracture at a T-score of -2.5) and in women with a prior fracture (and no information on BMD) |
| 5-Borgstrom (2010) [31] | Postmenopausal women aged over 50 years using FRAX | 2006 | Risedronate vs no treatment | Treatment was cost-effective (at a threshold of £30,000 per QALY) from the age of 65 years and at all ages in women who had previously sustained a fragility fracture. |
| 6-Borgstrom (2011) [14] | Postmenopausal women aged over 60 years using FRAX | 2008 | Bazedoxifene vs no treatment | ICER ranged from cost-saving (Sweden) to €105,450 (Spain) in 70-year-old women with a T-score of -2.5 and a prior fracture |
| 7-Borgstrom (2010) [37] | Women aged 70 years with T-score of -2.7 and 3.3 previous fractures (European Forsteo Observational Study) | 2007 | Teriparatide and PTH(1-84) vs no treatment | The cost per QALY gained of teriparatide vs. no treatment was estimated at €43,473 and PTH(1-84) was estimated at €104,396 |
| 8-Chau (2012) [32] | Women aged 72 years with T-score of -2.16 and 24% prevalent vertebral fracture (FREEDOM trial) | 2010 | Denosumab vs usual care (no therapy, alendronate, risedronate, raloxifene) | ICER for denosumab vs alendronate was CAN$60,266 and CAN$27,287 at high fracture risk |
| 9-Darbà (2013) [21] | Women aged 55-82 years with established osteoporosis and a high risk of fracture | 2010 | Bazedoxifene vs raloxifene | The ICER showed bazedoxifene to be the dominant treatment strategy |

| | | | | |
|---|---|---|---|---|
| 10-Ding (2008) [22] | Women aged 55 and over and treating with risedronate | 2002 | Risedronate vs no treatment | For women with a vertebral fracture in the previous 2 years, the costs per QALY gained were below a threshold of $100000 for women aged 70 years or older |
| 11-Fardellone (2010) [18] | Women with postmenopausal osteoporosis | 2007 | Zoledronic acid vs current treatment strategies | Costs per vertebral fracture avoided was €1497 vs €1685 |
| 12-Grima (2008) [40] | Postmenopausal women aged over 65 years | 2006 | Branded risedronate vs generic or branded alendronate | Incremental cost per QALY gained of CAN$3,877 for risedronate compared to generic alendronate |
| 13-Hiligsmann (2013) [51] | Women aged 70 years with T-score ≤-2.5 | 2010 | Bazedoxifene vs raloxifene | Treatments were equally cost-effective based on efficacy data from the overall clinical trial. In the subgroup analysis of women at higher risk of fractures, bazedoxifene was dominant in most of the simulations |
| 14-Hiligsmann (2010) [45] | Postmenopausal women aged over 75 years with T-score ≤-2.5 or with prevalent vertebral fracture (PVF) | 2006 | Strontium ranelate vs no treatment<br>Strontium ranelate vs risedronate | Strontium ranelate was dominant versus risedronate for women with osteoporosis aged over 75 years and for women with PVF aged 80 years. The cost per QALY gained of strontium ranelate compared with risedronate at 75 years of age was €11,435 for women with PVF |
| 15-Hiligsmann (2010) [49] | Postmenopausal women aged over 70 years with T-score ≤-2.5 or with prevalent vertebral fracture | 2006 | Strontium ranelate vs no treatment | For women with a T-score≤ -2.5, the costs per QALY gained of strontium ranelate were respectively €15,096 and €6,913 at 70 and 75 years of age while these values were €23,426 and €9,698 for women with prevalent vertebral fractures. At the age of 80 years, strontium ranelate was found to be cost-saving |
| 16-Hiligsmann (2009) [19] | Women aged 70 years with a twofold increase in the fracture risk of the average population | 2006 | Alendronate vs no treatment | ICER of €9,105 and €15,325 under full and realistic adherence assumptions, respectively |
| 17-Hiligsmann (2010) [41] | Women aged 65 years with a T-score of -2.5 | 2006 | Branded bisphosphonates (and generic alendronate) vs no treatment | The costs per QALY gained, for branded bisphosphonates (and generic alendronate), were estimated at €19,069 (€4,871), €32,278 (€11,985), and €64,052 (€30,181) for MPR values of 100, 80, and 60%, respectively, assuming real-world persistence. These values were €16,997 (€2,215), €24,401 (€6,179), and €51,750 (€20,569) for the same MPR than above, respectively, assuming full persistence. |
| 18-Hiligsmann (2010) [33] | Women aged 72 years, T-score of -2.2 and 23.6% with prevalent vertebral fracture (FREEDOM trial) | 2009 | Denosumab vs no treatment | The cost per QALY gained was €28,441. This value decreased to €15,532 and to €11,603 for women with a T-score of -2.5 or prevalent<br>vertebral fracture, respectively |

| | | | | |
|---|---|---|---|---|
| 19-Hiligsmann (2011) [42] | Postmenopausal women aged over 60 years with T-score ≤-2.5 or with prevalent vertebral fracture | 2009 | Densoumab vs oral bisphosphonates (branded risedronate, branded and generic alendronate) | Denosumab was cost effective compared with branded alendronate and risedronate at a threshold value of €30,000 per QALY.<br>The cost-effectiveness of denosumab compared with generic alendronate was estimated at €38,514, €22,220 and €27,862 per QALY for women aged 60, 70 and 80 years, respectively, with T-scores of -2.5 or less. |
| 20-Ivergard (2010) [38] | Postmenopausal women aged 55, 60 and 65 years using FRAX | 2008 | Raloxifene vs no treatment | The cost per QALY gained ranged from US$22,000 in women age 55 with 5% invasive breast cancer risk and 15–19.9% fracture probability, to $110,000 in women age 55 with 1% invasive breast cancer risk and 5–9.9% fracture probability |
| 21-Jansen (2008) [15] | Postmenopausal women aged over 50 years with a history of vertebral fracture and osteoporosis | 2004 | Alendronate/vitamin D3 vs no treatment, alendronate with dietary vitamin D supplements and ibandronate | In UK, alendronate/vitamin D3 was cost-effective compared to no treatment in women 70 years and older with osteoporosis (£17,439 per QALY gained).<br>Alendronate/vitamin D3 was cost-saving relative to alendronate with dietary supplements.<br>Relative to ibandronate, alendronate/vitamin D3 was cost-effective in women 50 years (£19 095 per QALY gained) and economically dominant in women 60 years or older.<br>Comparable results were observed for the Netherlands. |
| 22-Jonsson (2011) [43] | Typical Swedish patient population (women aged 71 years, T-score ≤-2.5 and a prevalence of morphometric vertebral fractures of 34%) | 2008 | Denosumab vs generic alendronate, branded risedronate, strontium ranelate and no treatment | The base-case ICERs were estimated at €27,000, €12,000, €5,000, and €14,000, for denosumab compared with generic alendronate, risedronate, strontium ranelate, and no treatment, respectively. |
| 23-Kanis (2008) [26] | Postmenopausal women aged over 50 years with different fracture risks | NR | Generic alendronate vs no treatment | Using a threshold of £30,000 and £20,000 per QALY, alendronate was cost-effective for the primary prevention of fracture in women with osteoporosis irrespective of age. |
| 24-Kanis (2008) [27] | Postmenopausal women aged over 50 years using FRAX | NR | Generic alendronate vs no treatment | Using a threshold of £20,000/QALY gained, treatment was cost effective at all ages when the 10-year probability of a major fracture exceeded 7%. |
| 25-Kim (2014) [16] | Postmenopausal women aged over 55 years using FRAX | 2008 | Bazedoxifene vs raloxifene | Bazedoxifene was cost-saving in all countries. |
| 26-Lekander (2008) [17] | Postmenopausal women at a T-score of -2.5 | 2006 | Hormone therapy vs no treatment | Hormone therapy was cost-effective for most sub-groups of hysterectomised women, whereas for women with an intact uterus without a previous fracture, hormone therapy was commonly dominated by no treatment. |

| | | | | |
|---|---|---|---|---|
| 27-Lekander (2009) [67] | Women with menopausal symptoms aged over 50 years | 2006 | Hormone therapy vs no treatment | The ICER for women with intact uterus was $2,803, and for hysterectomized women was $295 |
| 28-Lippuner (2012) [46] | Women aged over 50 years with different fractures probabilities | 2008 | Branded alendronate vs no treatment | Assuming a willingness to pay at 2 time Gross Domestic Product per capita, branded alendronate was cost-effective with a 10-year probability for a major osteoporotic fracture at or above 13.8% (range 10.8% to 15.0%) |
| 29-Moriwaki (2013) [68] | Osteopenic postmenopausal women aged over 65 years without a history of fracture | 2012 | Alendronate vs no treatment | The ICER of alendronate was $227,905 per QALY gained in women without risk factors; $92,937 per QALY gained in women with family history of hip fracture; $126,251 in women with alcohol intake ( >2units per day) and $129,067 currently smoking. |
| 30-Murphy (2012) [50] | Patients with a BMD T-score of -3.0, a historical vertebral fracture and an incidence vertebral fracture and patients with a BMD T-score of -3.0 and an incidence vertebral | 2012 | Teriparatide vs bisphosphonate | The ICERs were €36,995 and €19,371 per QALY gained in the two populations. |
| 31-Parthan (2013) [44] | Overall post-menopausal population and high-risk subrgoups | 2012 | Denosumab vs generic alendronate, branded risedronate and branded ibandronate | ICER of denosumab vs generic alendronate was $70,400 and $7,900 in the overall population and high risk subgroup, respectively. Risedronate and ibandronate were dominated by denosumab. |
| 32-Pham (2011) [28] | Cohort of women with various life expectancies beginning osteoporosis treatment between the age of 50 and 90 years | 2008 | Bisphosphonate vs no treatment | In the healthiest group, all costs were less than $18,000 per QALY. In the median quartiles of life expectancy, lifetime costs per QALY were less than $27,000 for patients at all ages; treatment became cost-saving at a starting age of 75 and remained so through a starting age of 85. |
| 33-Salpeter (2009) [29] | 50-year-old and 65-year-old women given hormone therapy or no therapy | 2006 | Hormone therapy vs no treatment | Hormone therapy in the younger cohort resulted in an incremental cost of $2438 per QALY gained. In the older cohort, hormone therapy resulted in a cost of $27,953 per QALY gained. |
| 34-Seeman (2010) [34] | Subgroups of patients over 80 years of age with osteoporosis from the SOTI and TROPOS trials | 2006 | Strontium ranelate vs no treatment | Strontium ranelate was cost-saving |
| 35-Strom (2010) [47] | Women aged 70 year with prior fracture and various T-score using FRAX | 2008 | Bazedoxifene vs no treatment | The ICER ranged from €37,443 (T-score of -1.5) to cost-saving (from T-score of -3) |

| | | | | |
|---|---|---|---|---|
| 36-Strom (2013) [39] | Postemnopausal women aged over 50 years at different degrees of osteoporotic fracture risk | 2010 | Denosumab vs no treatment, generic alendronate, risedronate and strontium ranelate | At a willingness-to-pay of £30,000 per QALY and a 10-year fracture probability equivalent to a woman with a prior fragility fracture, denosumab was cost-effective compared to no treatment from the age of 70 years. Denosumab was estimated to cost-effectively replace strontium, risedronate and generic alendronate at 10-year probabilities exceeding 11, 19 and 32 %, respectively. |
| 37-Thompson (2010) [23] | Postmenopausal women 65 years of age or older with a T-score ≤ -2.5 | 2008 | Branded risedronate with generic alendronate | Risedronate was cost-saving. |
| 38-Tosteson (2008) [24] | 4 risk groups among women with a T-score ≤ -2.5 | 2005 | No treatment, risedronate, alendronate, ibandronate, and teriperatide | The ICER of risedronate compared with no therapy ranged from cost saving for the base case to $66,722 per QALY for women aged 65 years with no previous fracture. Ibandronate and PTH were dominated in all risk groups |
| 39-Wasserfallen (2008) [48] | Women aged 70 years with established osteoporosis and previous vertebral fracture | 2005 | Risedronate vs no treatment | Risedronate was dominant |

*ICER Incremental Cost-Effectiveness Ratio, MPR Medical Possesion Ratio, PVF Prevalent Vertebral Fracture, QALY Quality Adjusted Life-Year*

**Table 3.a|** *Quality of reporting of cost-effectiveness analyses of drugs for postmenopausal osteoporosis using CHEERS checklist (articles 1-19)*

| | | Article Ref | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Item No** | **[13]** | **[25]** | **[20]** | **[36]** | **[31]** | **[14]** | **[37]** | **[32]** | **[21]** | **[22]** | **[18]** | **[40]** | **[51]** | **[45]** | **[49]** | **[19]** | **[41]** | **[33]** | **[42]** |
| **Title and abstract** | | | | | | | | | | | | | | | | | | | | |
| Title | 1 | Yes | Part | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | Yes | Yes |
| Abstract | 2 | Part | Part | Yes | Part | Part | Yes | Part | Yes | Part | Yes | Part | Yes | Yes | Yes | Yes | Part | Part | Yes | Yes |
| **Introduction** | | | | | | | | | | | | | | | | | | | | |
| Background and objectives | 3 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | Yes | Part | Part | Yes | Yes | Yes | Yes | Yes | Yes |
| **Methods** | | | | | | | | | | | | | | | | | | | | |
| Target population and subgroups | 4 | Part | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Setting and location | 5 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | Yes | Part | Yes | Yes | Yes | Yes | Part | Part | Yes | Yes |
| Study perspective | 6 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Comparators | 7 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | Yes | Yes | Yes | Yes | Yes | Yes | Part | Yes | Yes | Yes |
| Time horizon | 8 | Yes | Part | Part | Part | Part | Part | Part | Part | Part | Part | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Discount rate | 9 | Yes | Yes | No | Yes | Yes | Yes | Part | Yes | Yes | Part | No | Yes | Yes | Yes | Part | Yes | Yes | Yes | Yes |
| Choice of health outcomes | 10 | Part | Yes | Yes | Part | Part | Yes | Part | Part | Yes | Part | Yes | Yes | Part | Yes | Yes | Part | Yes | Yes | Yes |
| Measurement of effectiveness | 11a | Yes | NA | NA | Part | NA | Part | Yes | Part | NA | NA | NA | Yes | Yes | NA | Yes | NA | NA | Part | NA |
| | 11b | NA | Part | Part | NA | Yes | NA | NA | NA | Yes | Part | Part | NA | NA | Yes | NA | Part | Yes | NA | Part |
| Measurement and valuation of preference based outcomes | 12 | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part |
| Estimating resources and costs | 13a | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| | 13b | Yes | Part | Part | Part | Part | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | Part | Yes | Yes | Yes |
| Currency, price date, and conversion | 14 | Part | Yes | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Yes | Part | Part | Part | Part | Part | Part |
| Choice of model | 15 | Yes | Part | Part | Yes | Yes | Yes | Part | Part | Yes | Part | Yes | Yes | Part | Part | Yes | Yes | Part | Yes | Yes |
| Assumptions | 16 | Yes | Yes | Part | Yes | Yes | Yes | No | Yes | Part | Yes | Part | Yes | Yes | Part | Part | Yes | Yes | Part | Part |
| Analytical methods | 17 | Part | Part | Part | Part | Part | Yes | Part | Yes | Part | Part | Part | Part | Part | Yes | Yes | Yes | Part | Part | Yes |

| | | Article Ref | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Item No** | **[13]** | **[25]** | **[20]** | **[36]** | **[31]** | **[14]** | **[37]** | **[32]** | **[21]** | **[22]** | **[18]** | **[40]** | **[51]** | **[45]** | **[49]** | **[19]** | **[41]** | **[33]** | **[42]** |
| **Results** | | | | | | | | | | | | | | | | | | | | |
| Study parameters | 18 | Part | Yes | Yes | No | No | Yes | Part | Part | NA | Part | No | Yes | Part | Part | No | Yes | Part | Part | Part |
| Incremental costs and outcomes | 19 | Part | Yes | Yes | Part | Part | Yes | Yes | Yes | Yes | Part | Yes | Yes | No | Yes | Yes | Part | No | Yes | Yes |
| Characterising uncertainty | 20a | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| | 20b | Yes | Yes | Yes | Part | Yes | Yes | Yes | Yes | Part | Yes | Part | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Characterising heterogeneity | 21 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Discussion** | | | | | | | | | | | | | | | | | | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Yes | Yes | Part | Yes | Yes | Yes | Part | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Other** | | | | | | | | | | | | | | | | | | | | |
| Source of funding | 23 | Part | No | Part | Yes | Part | Part | Part | Yes | Part | Part | Part | Part | Part | Yes | Yes | Part | Yes | Yes | Yes |
| Conflicts of interest | 24 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| ***Scoring*** | | *20* | *19* | *18* | *18* | *18.5* | *21.5* | *17.5* | *20.5* | *15.5* | *17* | *15.5* | *20.5* | *18.5* | *21.5* | *20.5* | *18* | *19* | *21* | *21* |

**Table 3.b|** *Quality of reporting of cost-effectiveness analyses of drugs for postmenopausal osteoporosis using CHEERS checklist (articles 20-39)*

| | | Article Ref | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Item No** | **[38]** | **[15]** | **[43]** | **[26]** | **[27]** | **[16]** | **[17]** | **[67]** | **[46]** | **[68]** | **[50]** | **[44]** | **[28]** | **[29]** | **[34]** | **[47]** | **[39]** | **[23]** | **[24]** | **[48]** |
| **Title and abstract** | | | | | | | | | | | | | | | | | | | | | |
| Title | 1 | Yes | Yes | Yes | Yes | Part | Yes | Yes | Part | Part | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| Abstract | 2 | Part | Part | Part | Part | Part | Yes | Part | Part | Part | Part | Part | Yes | Part | Part | No | Part | Yes | Yes | Yes | Part |
| **Introduction** | | | | | | | | | | | | | | | | | | | | | |
| Background and objectives | 3 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | No | Part | Part | Yes | Yes | Part | Yes |
| **Methods** | | | | | | | | | | | | | | | | | | | | | |
| Target population and subgroups | 4 | Yes | Part | Yes | Part | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Part | Part | Yes | Part | Part | Yes | Yes | Yes | Yes |
| Setting and location | 5 | Yes | Yes | Part | No | Yes | Part | Yes | Yes | Yes | Yes | Yes | Yes | Part | Part | No | Yes | Yes | Part | Yes | Yes |
| Study perspective | 6 | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Comparators | 7 | Yes | Yes | No | Part | Yes | Yes | Yes | Yes | Yes | Part | Yes | Yes | No | Yes | Part | Part | Part | Part | Yes | Part |
| Time horizon | 8 | Part | Part | Part | Yes | No | Part | Part | Part | No | Part | Part | Part | Yes | Part | Part | Yes | Yes | Yes | Part | Part |
| Discount rate | 9 | Yes | Part | Yes | Yes | No | Yes | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Yes | Part | Part | Part |
| Choice of health outcomes | 10 | Yes | Yes | Part | Yes | Part | Yes | Yes | Yes | No | Part | Part | Yes | Part | Part | Yes | Yes | Yes | Yes | Part | Part |
| Measurement of effectiveness | 11a | Part | Yes | NA | NA | NA | Part | Part | Part | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| | 11b | NA | NA | Part | Yes | Part | NA | NA | NA | Part | Part | Part | Part | Part | Yes | No | Part | Part | Part | Part | Part |
| Measurement and valuation of preference based outcomes | 12 | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | Yes | Part | Part | Part | Part | Part | Part | Part | Part |
| Estimating resources and costs | 13a | NA | NA | NA | NA | No | NA | NA | NA | NA | NA | NA | NA | Part | NA | No | NA | Part | Part | NA | NA |
| | 13b | Part | Part | Yes | Yes | Part | Part | Part | Part | Part | Part | Part | Part | Part | Part | No | Part | Part | Yes | Yes | Yes |
| Currency, price date, and conversion | 14 | Part | Part | Part | Part | No | Part | Yes | Yes | Yes | Yes | Part | Yes | Part | Part | No | No | Part | Part | Part | Part |
| Choice of model | 15 | Part | Part | Part | Part | Yes | Yes | Part | Part | Part | Yes | Yes | Part | Part | Part | Part | Part | Part | Yes | Part | Part |
| Assumptions | 16 | Part | Part | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Part | Part | Part | Yes | Yes |
| Analytical methods | 17 | Part | Part | Part | No | No | Part | Part | Part | Part | Part | Part | Part | Yes | Yes | No | Part | No | Yes | Yes | Yes |

| | | Article Ref | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Item No** | **[38]** | **[15]** | **[43]** | **[26]** | **[27]** | **[16]** | **[17]** | **[67]** | **[46]** | **[68]** | **[50]** | **[44]** | **[28]** | **[29]** | **[34]** | **[47]** | **[39]** | **[23]** | **[24]** | **[48]** |
| **Results** | | | | | | | | | | | | | | | | | | | | | |
| Study parameters | 18 | Part | Part | Part | Part | Part | Part | Yes | Yes | No | Yes | Part | Part | Yes | Part | No | Part | Part | Part | Part | Part |
| Incremental costs and outcomes | 19 | Part | Yes | Yes | Part | No | Yes | Yes | Part | Part | Yes | Yes | Yes | Part | Yes | Part | No | Part | Yes | Yes | Yes |
| Characterising uncertainty | 20a | NA | NA | NA | NA | NA | NA | No | NA | No | NA | NA | NA | NA | No | NA | NA | NA | NA | NA | NA |
| | 20b | Yes | Yes | Yes | Yes | Part | Yes | Yes | Yes | Part | Yes | Yes | Yes | Yes | Part | No | No | Part | Yes | Yes | Yes |
| Characterising heterogeneity | 21 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes |
| **Discussion** | | | | | | | | | | | | | | | | | | | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Yes | Yes | Yes | Yes | Yes | Part | Yes | Part | Yes | Yes | Yes | Yes | Yes | Part | Part | Part | Yes | Yes | Yes | Part |
| **Other** | | | | | | | | | | | | | | | | | | | | | |
| Source of funding | 23 | Part | Sub | Part | Yes | Yes | Part | No | Part | Yes | Part | Yes | Yes | Yes | Yes | Part | Part | Yes | Yes | Part | Part |
| Conflicts of interest | 24 | No | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Part | Yes | No |
| ***Scoring*** | | *17* | *16.5* | *17.5* | *18* | *13* | *19* | *18* | *18* | *15* | *19* | *18* | *20* | *17.5* | *17* | *7* | *14* | *18.5* | *19* | *19* | *17* |

*RESULTS OF THE QUALITY OF REPORTING ASSESSMENT*

The results of the assessment of reporting quality per study is summarized in Tables 3.a and 3.b. Figure 2 shows for each item the proportion of studies reported completely adequate, partially or not at all. The most frequent partially or not reported items were 'measurement of effectiveness' (i.e. description of the methods used for the identification of studies used for effectiveness; items 11a and 11b), 'measurement and valuation of preferences based outcomes' (i.e. description of the population and methods used to elicit preferences for outcomes; item 12), 'currency, price date and conversion' (i.e. reporting of the dates of the estimated resource quantities and unit costs and description of the methods for adjusting estimated unit costs to the year of reported costs; item 14) and 'analytic methods' (i.e. description of all structural or other assumptions underpinning the decision-analytic model; item 17). The reporting in the abstract could be improved (item 2). In addition, perspective, setting, methods and results of uncertainty analyses were not always included while comparators were sometimes considered without (proper) justification. Justification for time horizon, discount rates and choice for health outcomes were also not provided in all articles. The description of approaches used to estimate resources and costs, as well as the reporting of study parameters including values, ranges, references, and if used, probability distributions for all parameters was also not complete in several articles. Studies generally provided incremental costs and outcomes (item 19), characterize uncertainty and heterogeneity (items 20 and 21) and discuss the key findings, limitations, generalizability and how the findings fit with current knowledge (item 22), although several articles did not satisfactory fulfil these criteria. The source of funding and the role of the funder in the identification, design, conduct, and reporting of the analysis was only fully reported in about half of the articles. Substantial differences in the quality of reporting were observed between articles with an average score of 17.9 out of 24 (range from 7 to 21.5). Average score was higher for articles published in 2011-2013 (score of 18.3) in comparison to articles published in 2008-2010 (score of 17.3). European studies reported an average score of 17.7 (with a mean score of 19.8 for the 8 studies conducted in Belgium) while studies using a US/Canada perspective had an average score of 18.6. Articles published in health economic journals (see section 3.2 for group classification) have a higher reporting score (score of 19.5) than articles published in osteoporosis journals (score of 17.6).

*KEY DRIVERS OF COST-EFFECTIVENESS*

Several key drivers of cost-effectiveness were identified during the systematic review. They are discussed below and include individual fracture risk, medication adherence, selected comparators and country-specific analyses.

Individual fracture risk

The cost-effectiveness of osteoporotic drugs substantially improves with increasing fracture risk and the age of the population, the latter partly due to higher admission rates in nursing home avoided. So, for example, the cost-effectiveness of denosumab in women with BMD T-score ≤-2.5 was estimated at €25,061 and €8,948 per QALY gained at the ages of 60 and 70 years, respectively (year 2010 value) [33]. At the age of 80 years, denosumab became cost-saving. Other studies show cost-effectiveness varies across populations with different risk for future fractures. For example, in women aged 70 years, the cost-effectiveness of strontium ranelate ranged from £34,200 to £13,800 (year 2006 value) per QALY gained according to BMD T-score [36]. Parthan et al. [44] also showed that the incremental cost-effectiveness ratio (ICER) of denosumab versus generic alendronate was $70,400 and $7,900 (year 2012 value) in the overall population and high risk subgroup, respectively.

Medication adherence

Medication adherence has emerged as an important perspective in cost-effectiveness analyses in osteoporosis [52, 53]. Adherence with osteoporosis medications has been shown to be poor and suboptimal [54], leading to a decrease in treatment effectiveness [55]. As a consequence, poor adherence alters the cost-effectiveness of drug therapies [52]. In Hiligsmann et al. [41], the costs per QALY gained for branded bisphosphonates were estimated at €19,069, €32,278 and €64,052 (year 2006 value) for adherence level of 100%, 80%, and 60%, respectively. When comparing drugs with potential differences in medication adherence and persistence, the lack of inclusion of these concepts could potentially bias the results. Hiligsmann et al. [42, 52] suggests that, if adherence was not included, the cost-effectiveness of denosumab compared with oral bisphosphonates would have been less favourable.

Comparators

An increasing number of studies used active comparators in cost-effectiveness analyses of drugs in postmenopausal osteoporosis. Seventeen of the 39 studies (43.7%) included at least one active comparator, in comparison with 1 of the 22 studies (4.6%) published between 2002 and 2005 [5]. The cost-effectiveness of a drug therapy could differ according to the selected comparator. In Parthan et al. [44], in the overall population, denosumab was always dominant compared with risedronate and ibandronate, while the cost-effectiveness was less favorable when using generic alendronate as comparator. Justification of the comparators is therefore becoming important. Interpretation of cost-effectiveness analyses between active comparators requires some caution. For most of these analyses, indirect comparisons were required to estimate cost-effectiveness since there is limited trial data directly comparing effectiveness between drugs.

Country-specific analyses

The cost-effectiveness of osteoporotic drugs differed markedly between countries. In a study assessing the cost-effectiveness of bazedoxifene in 6 European countries [14], the ICER ranged from €105,450 in Spain to cost-saving in Sweden (year 2008 value). This difference was explained to a large extent by regional differences in fracture risk [14]. Marked variation in the incidence of fractures among world regions is recongnized [56]. Additional factors such as fracture cost, drug cost and medication adherence could also differ between countries, and hence affect the cost-effectiveness of drug therapies. Yearly medication costs ranged between €325 and €540 in the 6 European countries [14], while the costs of hip fracture were between €10,142 and €18,923 (year 2008 value).

## DISCUSSION

Our systematic review identified 39 economic evaluations of drugs in postmenopausal osteoporosis published between 2008 and 2013. When compared with no treatment, active osteoporotic drugs were generally cost-effective, at commonly-accepted thresholds for cost-effectiveness (around €45,000 per QALY gained), in postmenopausal women aged over 60-65 years with low bone mass, especially those with prior vertebral fractures. In view of the heterogeneity in fracture risk, comparators, country setting, model structure and incorporation of medication adherence, and given the lack of head-to-head comparisons, it is not yet possible to make clear recommendations on the cost-effectiveness between drugs.

Our review updates prior systematic reviews of economic evaluations conducted in osteoporosis [4, 57, 5, 58]. Fleurence et al. [4] identified 23 economic evaluations of oral bisphosphonates between 1990 and May 2006 while Zethraeus et al. [5] analyzed 22 articles about the cost-effectiveness of the prevention and treatment of osteoporosis published in the period 2002–2005. These reviews already suggested that oral bisphosphonates were cost-effective in women aged over 70 years, particularly those with additional risk factors. In addition to oral bisphosphonates, our review reveals that new alternative treatments (such as denosumab, strontium ranelate, bazedoxifene, zoledronic acid) can also be considered as cost-effective as compared with placebo. Additional countries and patient populations have been identified in recent economic evaluations. More recently, Si et al. [12] carried out a systematic review (until May 2013) of the evolution of health economic models used in osteoporosis. In contrast with this study, we restricted our analysis to drug therapies, described and discussed the results of the studies, and provided a critical appraisal of all the articles.

In line with prior studies, some key drivers of the cost-effectiveness were found in our review. First, the consideration of patient characteristics is highly important. The development of several fracture

risk algorithm such as FRAX enables the estimation of the cost-effectiveness in various types of patients with different combinations of clinical risk factors. Second, medication adherence affects the cost-effectiveness of interventions in osteoporosis and should therefore be incorporated in future economic evaluations. Assessing adherence (from randomized controlled trials, observational studies or claims data) and incorporating them in cost-effectiveness analyses could however be challenging [52, 53]. The authors should recognize potential limitations of adherence data and use sensitivity analyses. Third, indirect or mixed treatment comparisons are becoming a familiar feature of technology appraisals at the National Institute of Clinical and Care Excellence in UK, just as they make a frequent appearance in leading clinical journals [59]. In our review, relatively few economic evaluations included all potential relevant interventions in their analysis. Indirect comparisons require correct methodological approaches to adjust between studies or differences in characteristics of studies populations. The ISPOR's Task Force on Indirect comparisons provides guidance on technical aspects of conducting network meta-analyses and indirect comparisons [60]. Fourth, the transferability of economic evaluations is uncertain since many factors such as fracture risk could differ between countries and therefore affects the cost-effectiveness. Cost-effectiveness should therefore be evaluated at the national level. Additional key issues for economic evaluations in osteoporosis were recently identified by Stevenson et al. [61].

With regard to the quality of reporting of these economic evaluations, despite the fact that guidelines for conducting health economic evaluations are widely available for many years and previous reviews have already criticized economic evaluations for poor reporting, we observed that quality of reporting is still largely insufficient for several articles. Several items were partially or not reported by most articles. These include the methods used for the identification and synthesis of clinical effectiveness data, the description of the population and methods use to value preferences based outcomes, the reporting of the dates of the estimated resource quantities and unit costs, and all analytic methods supporting the evaluation including by example approaches to validate the model or methods for handling population heterogeneity and uncertainty. We hope that the availability of the CHEERS statement [10, 11] will lead to improve the reporting and hence the quality of economic evaluations of osteoporosis. To improve the comparability and quality of health economic evaluation in osteoporosis, defining minimal methodological and structural requirements that could be transferable to any specific decision-making context will be an additional step forward [17].

Although we followed recommendations for conducting reviews of economic evaluations, [62], there may have some potential limitations to our study First, many reviewers were involved in the quality of reporting assessment and differences in scoring could potentially be due to interpretation of reviewers. Differentiating between partially or fully reported was difficult for some items. Second, we assigned a score of 0.5 for partial reporting which could be questionable and lead to an

upgrade of the overall score of the studies. Using a binary rating (yes when the item was completely reported and no otherwise) would have decreased the reporting quality. Third, level of quality may be underestimated for studies in which some of the items were not easily applicable or were reported elsewhere. Several articles referred explicitly to previously published articles where more information could be available, and some articles had different objectives than assessing the cost-effectiveness of drugs. By example, the main aim of the article of Kanis et al. [27] was to determine intervention thresholds, based on cost-effectiveness estimates of alendronate. Fourth, it should be acknowledged that poor reporting does not necessarily lead to poor quality and results bias. In our review, we have not assessed the methodological quality of the articles. An evaluation of the modelling quality of these studies using by example the Philips checklist would be interesting [63]. Finally, to identify key drivers of cost-effectiveness, we did not perform a systematic quantitative assessment.

A majority of studies (30/39 articles) were funded by pharmaceutical industries. While research has found that studies funded by industry were more likely to report favorable cost-effectiveness ratios [64], a review conducted in osteoporosis revealed that funding source (industry versus non-industry) did not seem to significantly affect the reporting of favourable cost-effectiveness for bisphosphonates [65].

The results of our review could be important for decision makers when prioritizing health interventions. With the increasing use of economic data in health-care decision making (especially for reimbursement of drugs), the increasing burden of osteoporosis [1] and the recent development of new drug interventions [6], consideration of the cost-effectiveness of anti-osteoporosis medications is becoming increasingly important. Alongside cost-effectiveness, other factors such as affordability could also play a role in reimbursement decisions. Insights into the preferences of patients groups should also be taken into account alongside medical and economic considerations. A recent discrete-choice experiment revealed that patients could have preferences for attributes of osteoporosis drug therapy [66].

In conclusion, this review found an increasing number of published cost-effectiveness analyses of drug in osteoporosis. Active osteoporotic drugs are generally cost-effective, when compared with no treatment, in postmenopausal women aged over 60-65 years with low bone mass, especially those with prior vertebral fractures. Future economic evaluations in osteoporosis should take into consideration the patient characteristics as well as medication adherence. More attention should also be given to the methods used for the identification and synthesis of clinical effectiveness data, especially now there is an increasing need for comparative cost-effectiveness studies. Improving the quality of reporting of economic evaluations is also needed.

## KEY POINTS FOR DECISION MAKERS

- Active osteoporotic drugs were generally cost-effective in postmenopausal women aged over 60-65 years with low bone mass, especially those with prior vertebral fractures.
- In view of the heterogeneity in fracture risk, comparators, country setting, model structure and incorporation of medication adherence, and given the lack of head-to-head comparisons, it is not yet possible to make clear recommendations between drugs in terms of cost-effectiveness.
- Despite the fact that guidelines for conducting health economic evaluations are widely available for many years, we observed that quality of reporting is still largely insufficient for several articles.

## ACKNOWLEDGEMENTS

No funding has been received for the conduct of this study and/or preparation of this manuscript.

## REFERENCES


1. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, 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.
2. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465-75.
3. Hiligsmann M, Kanis JA, Compston J, Cooper C, Flamion B, Bergmann P, et al. Health technology assessment in osteoporosis. Calcif Tissue Int. 2013;93(1):1-14.
4. Fleurence RL, Iglesias CP, Johnson JM. The cost effectiveness of bisphosphonates for the prevention and treatment of osteoporosis: a structured review of the literature. Pharmacoeconomics. 2007;25(11):913-33.
5. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis--a review of the literature and a reference model. Osteoporos Int. 2007;18(1):9-23.
6. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24(1):23-57.
7. Body JJ, Bergmann P, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. Osteoporos Int. 2010;21(10):1657-80.
8. Hiligsmann M, Boonen A, Dirksen CD, Ben Sedrine W, Reginster JY. Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporotic women. Expert Rev Pharmacoecon Outcomes Res. 2013;13(1):19-28.
9. Hiligsmann M, Vanoverberghe M, Neuprez A, Bruyere O, Reginster JY. Cost-effectiveness of strontium ranelate for the prevention and treatment of osteoporosis. Expert Rev Pharmacoecon Outcomes Res. 2010;10(4):359-66.
10. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Value Health. 2013;16(2):e1-5.
11. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Pharmacoeconomics. 2013;31(5):361-7.
12. Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. Osteoporos Int. 2014;25(1):51-60.
13. Akehurst R, Brereton N, Ariely R, Lusa T, Groot M, Foss P, et al. The cost effectiveness of zoledronic acid 5 mg for the management of postmenopausal osteoporosis in women with prior fractures: evidence from Finland, Norway and the Netherlands. J Med Econ. 2011;14(1):53-64.
14. Borgstrom F, Strom O, Kleman M, McCloskey E, Johansson H, Oden A, et al. Cost-effectiveness of bazedoxifene incorporating the FRAX(R) algorithm in a European perspective. Osteoporos Int. 2011;22(3):955-65.

15. Jansen JP, Gaugris S, Bergman G, Sen SS. Cost-effectiveness of a fixed dose combination of alendronate and cholecalciferol in the treatment and prevention of osteoporosis in the United Kingdom and The Netherlands. Curr Med Res Opin. 2008;24(3):671-84.
16. Kim K, Svedbom A, Luo X, Sutradhar S, Kanis JA. Comparative cost-effectiveness of bazedoxifene and raloxifene in the treatment of postmenopausal osteoporosis in Europe, using the FRAX algorithm. Osteoporos Int. 2014;25(1):325-37.
17. Lekander I, Borgstrom F, Strom O, Zethraeus N, Kanis JA. Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK--results based on the Women's Health Initiative randomised controlled trial. Bone. 2008;42(2):294-306.
18. Fardellone P, Cortet B, Legrand E, Bresse X, Bisot-Locard S, Vigneron AM, et al. Cost-effectiveness model of using zoledronic acid once a year versus current treatment strategies in postmenopausal osteoporosis. Joint Bone Spine. 2010;77(1):53-7.
19. Hiligsmann M, Ethgen O, Bruyere O, Richy F, Gathon HJ, Reginster JY. Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. Value Health. 2009;12(5):687-96.
20. Berto P, Maggi S, Noale M, Lopatriello S. Risedronate versus alendronate in older patients with osteoporosis at high risk of fracture: an Italian cost-effectiveness analysis. Aging Clin Exp Res. 2010;22(2):179-88.
21. Darba J, Perez-Alvarez N, Kaskens L, Holgado-Perez S, Racketa J, Rejas J. Cost-effectiveness of bazedoxifene versus raloxifene in the treatment of postmenopausal women in Spain. Clinicoecon Outcomes Res. 2013;5:327-36.
22. Ding H, Koinuma N, Stevenson M, Ito M, Monma Y. The cost-effectiveness of risedronate treatment in Japanese women with osteoporosis. J Bone Miner Metab. 2008;26(1):34-41.
23. Thompson M, Pasquale M, Grima D, Moehrke W, Kruse HP. The impact of fewer hip fractures with risedronate versus alendronate in the first year of treatment: modeled German cost-effectiveness analysis. Value Health. 2010;13(1):46-54.
24. Tosteson AN, Burge RT, Marshall DA, Lindsay R. Therapies for treatment of osteoporosis in US women: cost-effectiveness and budget impact considerations. The American journal of managed care. 2008;14(9):605-15.
25. Alzahouri K, Bahrami S, Durand-Zaleski I, Guillemin F, Roux C. Cost-effectiveness of osteoporosis treatments in postmenopausal women using FRAX thresholds for decision. Joint Bone Spine. 2013;80(1):64-9.
26. Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. Bone. 2008;42(1):4-15.
27. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. Case finding for the management of osteoporosis with FRAX--assessment and intervention thresholds for the UK. Osteoporos Int. 2008;19(10):1395-408.
28. Pham AN, Datta SK, Weber TJ, Walter LC, Colon-Emeric CS. Cost-effectiveness of oral bisphosphonates for osteoporosis at different ages and levels of life expectancy. J Am Geriatr Soc. 2011;59(9):1642-9.
29. Salpeter SR, Buckley NS, Liu H, Salpeter EE. The cost-effectiveness of hormone therapy in younger and older postmenopausal women. American Journal of Medicine. 2009;122(1):42-52.

30. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. Osteoporos Int. 1994;4(6):368-81.
31. Borgstrom F, Strom O, Coelho J, Johansson H, Oden A, McCloskey EV, et al. The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX. Osteoporos Int. 2010;21(3):495-505.
32. Chau D, Becker DL, Coombes ME, Ioannidis G, Adachi JD, Goeree R. Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Canada. J Med Econ. 2012;15 Suppl 1:3-14.
33. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. Bone. 2010;47(1):34-40.
34. Seeman E, Boonen S, Borgstrom F, Vellas B, Aquino JP, Semler J, et al. Five years treatment with strontium ranelate reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life-years in women over 80 years of age. Bone. 2010;46(4):1038-42.
35. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385-97.
36. Borgstrom F, Strom O, Coelho J, Johansson H, Oden A, McCloskey E, et al. The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis. Osteoporos Int. 2010;21(2):339-49.
37. Borgstrom F, Strom O, Marin F, Kutahov A, Ljunggren O. Cost effectiveness of teriparatide and PTH(1-84) in the treatment of postmenopausal osteoporosis. J Med Econ. 2010;13(3):381-92.
38. Ivergard M, Strom O, Borgstrom F, Burge RT, Tosteson AN, Kanis J. Identifying cost-effective treatment with raloxifene in postmenopausal women using risk algorithms for fractures and invasive breast cancer. Bone. 2010;47(5):966-74.
39. Strom O, Jonsson B, Kanis JA. Intervention thresholds for denosumab in the UK using a FRAX(R)-based cost-effectiveness analysis. Osteoporos Int. 2013;24(4):1491-502.
40. Grima DT, Papaioannou A, Thompson MF, Pasquale MK, Adachi JD. Greater first year effectiveness drives favorable cost-effectiveness of brand risedronate versus generic or brand alendronate: modeled Canadian analysis. Osteoporos Int. 2008;19(5):687-97.
41. Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY. Potential clinical and economic impact of nonadherence with osteoporosis medications. Calcif Tissue Int. 2010;86(3):202-10.
42. Hiligsmann M, Reginster JY. Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. Pharmacoeconomics. 2011;29(10):895-911.
43. Jonsson B, Strom O, Eisman JA, Papaioannou A, Siris ES, Tosteson A, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. Osteoporos Int. 2011;22(3):967-82.
44. Parthan A, Kruse M, Yurgin N, Huang J, Viswanathan HN, Taylor D. Cost effectiveness of denosumab versus oral bisphosphonates for postmenopausal osteoporosis in the US. Appl Health Econ Health Policy. 2013;11(5):485-97.
45. Hiligsmann M, Bruyere O, Reginster JY. Cost-effectiveness of strontium ranelate versus risedronate in the treatment of postmenopausal osteoporotic women aged over 75 years. Bone. 2010;46(2):440-6.

46. Lippuner K, Johansson H, Borgstrom F, Kanis JA, Rizzoli R. Cost-effective intervention thresholds against osteoporotic fractures based on FRAX(R) in Switzerland. Osteoporos Int. 2012;23(11):2579-89.
47. Strom O, Borgstrom F, Kleman M, McCloskey E, Oden A, Johansson H, et al. FRAX and its applications in health economics--cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example. Bone. 2010;47(2):430-7.
48. Wasserfallen JB, Krieg MA, Greiner RA, Lamy O. Cost effectiveness and cost utility of risedronate for osteoporosis treatment and fracture prevention in women: a Swiss perspective. J Med Econ. 2008;11(3):499-523.
49. Hiligsmann M, Bruyere O, Reginster JY. Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women. Osteoporos Int. 2010;21(1):157-65.
50. Murphy DR, Smolen LJ, Klein TM, Klein RW. The cost effectiveness of teriparatide as a first-line treatment for glucocorticoid-induced and postmenopausal osteoporosis patients in Sweden. BMC Musculoskelet Disord. 2012;13:213.
51. Hiligsmann M, Ben Sedrine W, Reginster JY. Cost-effectiveness of bazedoxifene compared with raloxifene in the treatment of postmenopausal osteoporotic women. J Bone Miner Res. 2013;28(4):807-15.
52. Hiligsmann M, Boonen A, Rabenda V, Reginster JY. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. Expert Rev Pharmacoecon Outcomes Res. 2012;12(2):159-66.
53. Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. Osteoporos Int. 2011;22(10):2565-73.
54. Rabenda V, Hiligsmann M, Reginster JY. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. Expert Opin Pharmaco. 2009;10(14):2303-15.
55. Ross S, Samuels E, Gairy K, Iqbal S, Badamgarav E, Siris E. A meta-analysis of osteoporotic fracture risk with medication nonadherence. Value Health. 2011;14(4):571-81.
56. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23(9):2239-56.
57. Strom O, Borgstrom F, Sen SS, Boonen S, Haentjens P, Johnell O, et al. Cost-effectiveness of alendronate in the treatment of postmenopausal women in 9 European countries--an economic evaluation based on the fracture intervention trial. Osteoporos Int. 2007;18(8):1047-61.
58. Zethraeus N, Ben Sedrine W, Caulin F, Corcaud S, Gathon HJ, Haim M, et al. Models for assessing the cost-effectiveness of the treatment and prevention of osteoporosis. Osteoporos Int. 2002;13(11):841-57.
59. Fleurence RL, Iglesias CP, Torgerson DJ. Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. Osteoporos Int. 2006;17(1):29-40.
60. Ades AE. ISPOR states its position on network meta-analysis. Value Health. 2011;14(4):414-6.
61. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health. 2011;14(4):429-37.
62. Stevenson MD, Selby PL. Modelling the Cost Effectiveness of Interventions for Osteoporosis: Issues to Consider. Pharmacoeconomics. 2014. In press

63. Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. JAMA. 2002;287(21):2809-12.
64. Bell CM, Urbach DR, Ray JG, Bayoumi A, Rosen AB, Greenberg D, et al. Bias in published cost effectiveness studies: systematic review. BMJ. 2006;332(7543):699-703.
65. Fleurence RL, Spackman DE, Hollenbeak C. Does the funding source influence the results in economic evaluations? A case study in bisphosphonates for the treatment of osteoporosis. Pharmacoeconomics. 2010;28(4):295-306.
66. Hiligsmann M, Dellaert BG, Dirksen CD, van der Weijden T, Goemaere S, Reginster JY, et al. Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. Arthritis Res Ther. 2014;16(1):R36.
67. Lekander I, Borgstrom F, Strom O, Zethraeus N, Kanis JA. Cost-effectiveness of hormone therapy in the United States. J Womens Health (Larchmt). 2009;18(10):1669-77.
68. Moriwaki K, Komaba H, Noto S, Yanagisawa S, Takiguchi T, Inoue H, et al. Cost-effectiveness of alendronate for the treatment of osteopenic postmenopausal women in Japan. J Bone Miner Res. 2013;28(2):395-403.

CHAPTER 5

# THE IMPORTANCE OF INTEGRATING MEDICATION ADHERENCE INTO PHARMACOECONOMIC ANALYSES: THE EXAMPLE OF OSTEOPOROSIS

**Hiligsmann M**, Boonen A, Rabenda V, Reginster JY

*Expert Review of Pharmacoeconomics & Outcomes Research, 2012, 12(2), 159-66*

## ABSTRACT

Adherence with medications is poor and suboptimal in many chronic diseases. Non-adherence can reduce treatment effectiveness and can have impact on healthcare costs. As a consequence, it may alter the cost-effectiveness of drug therapies. This article emphasizes the importance of integrating medication compliance and persistence in pharmacoeconomic evaluations using osteoporosis as example. A limited number of studies carried out to date have suggested important economic implications of poor adherence with osteoporosis medications. Therefore, compliance and persistence should be an integral part of clinical studies and pharmacoeconomic analyses in order to estimate the cost-effectiveness of drug therapies in the current community practice. Measuring adherence and incorporating it into health economic modeling may, however, pose particular challenges.

### KEYWORDS

Adherence, compliance, cost-effectiveness, economic, osteoporosis, persistence.

## INTRODUCTION

Pharmacoeconomic evaluations are increasingly used in health care. By comparing costs and consequences of health interventions, economic evaluations can serve as a tool to help decision makers to efficiently allocate scarce resources. To conduct economic evaluations, researchers often obtained efficacy data from randomized clinical trials (RCTs). Although RCTs have, at least theoretically, high internal validity, they are associated with high levels of adherence compared with those observed in daily practice. The estimates of treatment efficacy and subsequently pharmacoeconomic results may therefore not be generalizable to current community practice. In order to estimate the cost-effectiveness of the intervention/drug in real-life settings, it is important that economic evaluations take adherence into account. Poor compliance and persistence will reduce the cost of the intervention, but at the same time might decrease the side-effects and the therapeutic potential of drug therapy in term of health effects and costs, and can therefore have substantial impact on the effectiveness and cost-effectiveness of drug therapies [1].

This study aims to highlight the importance of integrating medication adherence in pharmacoeconomic analyses, using osteoporosis as an example. Poor compliance and persistence are common problems in the treatment of osteoporosis. Approximately 75% of women in whom an oral bisphosphonates, currently the most widely medications prescribed for osteoporosis, is initiated, have been shown to be non-adherent within one year and 50% discontinued therapy by this time [2, 3]. A few studies carried out to date have suggested important economic implications of poor adherence to osteoporosis medications [4-8].

More specifically, the purposes of this article are (1) to present and illustrate, by a published example including reviews and single studies, the impacts of poor adherence with osteoporosis medications on effectiveness, healthcare costs and cost-effectiveness, (2) to review recent economic evaluations that have integrated compliance and persistence and (3) to discuss some important challenges for incorporating compliance and persistence in pharmacoeconomic analyses conducted in osteoporosis.

## DEFINITION AND MEASUREMENTS

Since a wide variety of definitions for medication adherence have been used in the literature, it is important to define the terminology. In line with the definitions issued by an expert consensus group in osteoporosis [9], medication adherence is used as a general term to cover medication compliance and persistence. Medication compliance may be defined as “the extent to which a patient acts in accordance with the prescribed interval, dose and dosing of regimen” and medication persistence as “the length of time from initiation to discontinuation of therapy” [10].

Medication compliance is typically expressed as the percentage of prescribed doses taken in relation to the study period, often called the medication possession ratio (MPR). Studies conducted in osteoporosis have estimated the mean MPR over a period of time (typically one year) and/or the probabilities of patients being highly or poorly compliant. A threshold of 80% has been most commonly used to define high compliance with osteoporosis treatments [11]. The definition of 'good compliance' is however arbitrary and difficult to evaluate. An empirical calculation of an optimal threshold for predicting fracture risk has been estimated at 68% [12].

Persistence is measured as the number of days on therapy or as a dichotomous variable (persistent or not) as to whether a patient continued therapy beyond an elapsed time period (e.g. 12 months). A threshold regarding discontinuation period have to be defined for measuring persistence. For daily or weekly treatment, a refill gap of 1 month is commonly considered to define non-persistence [13] but, as for MPR thresholds, there are no standardized definitions for non-persistence. Gap lengths for treatments with longer dosing intervals are less well defined, though a working group recently discussed that stopping treatment for 2 months may be a suitable definition for a monthly treatment, and a delay of more than 3 months in the case of yearly injections [13]. The operational definitions to measure compliance and persistence could therefore differ between studies and may impact on the results.

Medication compliance and persistence can be assessed using direct or indirect methods. Direct assessment methods (e.g. observation, serum drug concentration, biochemical analysis) are more accurate but are more costly and often impractical [14]. Indirect methods (e.g. retrospective prescription claims database) often constitute the only source available to assess adherence and an inexpensive way of collecting adherence [15]. Most studies assessing medication adherence have used pharmacy prescription refill records. This method however lacks the details of daily dosing (e.g. missing doses, wrong timing) and may underestimate medication non-adherence, and especially non-compliance.

## IMPACT OF POOR ADHERENCE ON ANTI-FRACTURE EFFECTIVENESS

Poor adherence reduces the effectiveness of osteoporosis treatment, resulting in lower bone mineral density gains and subsequently higher fractures rates [16]. Two meta-analyses were recently performed to assess the fracture risk among patients non-compliant versus compliant to therapy for osteoporosis [17, 18]. First, a meta-analysis of six articles, including 171,063 patients, suggested that the risk of fractures was 46% higher in non-compliant patients (MPR<80%) with bisphosphonate therapy compared with compliant patients [18]. The increased fracture risk in non-compliant patients was lower for non-vertebral (16%) and hip (28%) than for clinical vertebral fractures (43%). In another meta-analysis, constituting of 113,376 patients from 8 studies, of which the majority were retrospective database analyses considering the effect of adherence to

bisphosphonate therapy, fracture risk increased by approximately 30% in non-compliant patients (MPR <80%) compared with compliant patients [17].

Most of these studies have suggested a nonlinear relationship between MPR and fracture risk[11]. For example, a large US database showed no treatment benefit for compliance levels defined by an MPR <50% and then an exponential decrease of fractures rates as compliance increased [19]. Similarly, a German study observed no risk benefit with compliance levels of less than 60% [20]. Elsewhere, however, a linear relationship was observed between MPR (expressed as continuous variable) and the probability of hip fractures [21]. Each incremental decrease of 1% in compliance resulted in an increase by 0.4% of the risk of hip fracture [21].

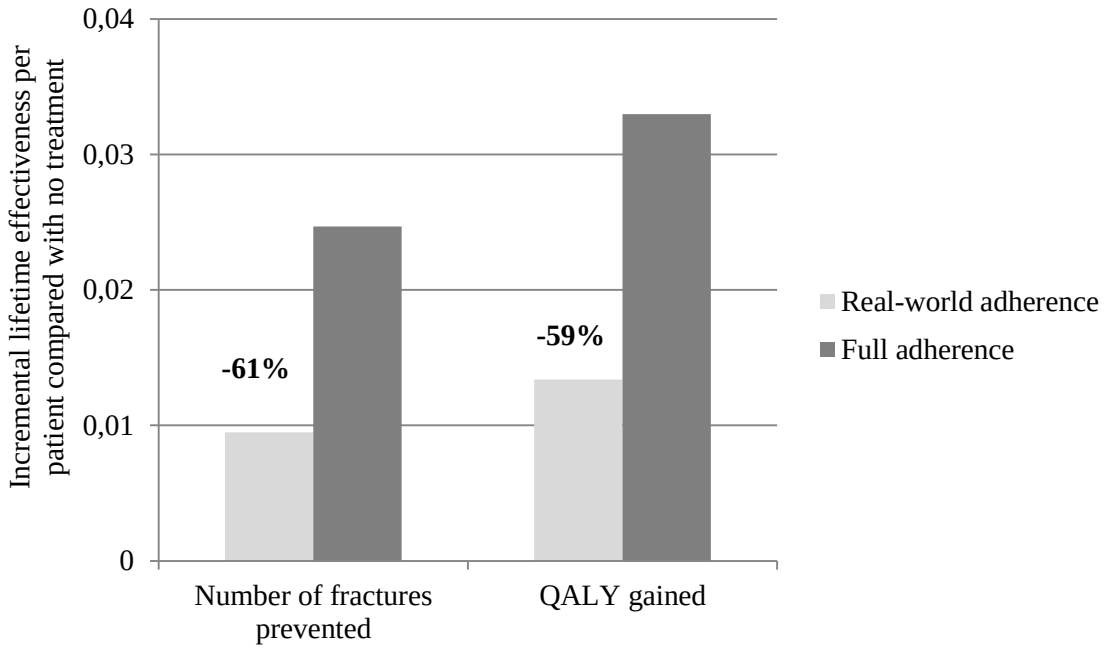
Non-persistence patients also reported higher fracture rates compared with persistent patients. A meta-analysis, including 57,334 patients from five studies, showed that non-persistence increases the risk of all fractures by 30% to 40% versus persistence [18]. A recent Swedish observational study also showed that the 3-year fracture incidence was related to time on treatment with osteoporosis medications [22]. Consistent with RCTs, this study shows that, in real-life settings, at least 6 months of treatment with oral bisphosphonates can reduce fracture incidence [22, 23]. No treatment effect could therefore be assumed for patients receiving drug therapy for less than 6 month.

The magnitude of the effects of medication adherence should be interpreted with some caution [24]. A limitation to the observational studies is the concern surrounding bias due to the "healthy adherer effect", which could lead to an overestimation of medication benefits. While the reduced effectiveness observed in non-compliant and non-persistent patients may be due to a true biological effect, it may also be at least partly caused by confounding factors due to differences between the types of patients who remain adherent versus those becoming non-adherent. In the Women's Health Initiative's study [24], adherence to placebo significantly reduced the risk of hip fracture by 50%. These results are however not supported by another study that shows no evidence of healthy adherer bias was shown in a frail cohort of seniors [25] and further exploration of the healthy adherer effect would be required in osteoporosis.

Acknowledging this potential limitation, poor adherence may be responsible for a large difference between efficacy and clinical effectiveness. The consequences of poor adherence on the clinical effectiveness at a population level have been shown to be significant in many countries [4, 6, 7, 26]. An example of the impact of medication adherence on effectiveness is provided on Figure 1. Using Belgian persistence and compliance data to alendronate, an oral bisphosphonate, [21] and simulation modeling [27], this study [4] compared the clinical and economic outcomes obtained at real-world adherence levels with those expected with full adherence over three years. Outcomes were expressed as the number of hip fractures and in quality-adjusted life-years (QALYs), which is an attractive outcome measurement for cost-effectiveness analyses that takes into account

reductions in both morbidity and mortality. The numbers of hip fractures prevented were 0.0095 and 0.0247 for the real-world and full adherence scenario, respectively [4]. Therefore, the number of hip fractures prevented in the case of real-world adherence represents only 38.5% of that estimated with full adherence scenario. The QALYs gain in the real-world adherence scenario was estimated at 40.6% to that obtained under full adherence scenario. More than half of the potential clinical benefits of oral bisphosphonates in patients with osteoporosis are therefore expected to be lost due to poor compliance and failure to persist. Sensitivity analysis has shown that the effect of non-adherence on clinical effectiveness was primarily driven by the issues of non-persistence, with more than 90% of the clinical burden of poor adherence resulting from non-persistence [4].

**Figure 1|** *Impact of medication non-adherence on the clinical effectiveness (expressed as number of fractures prevented and quality-adjusted life-year (QALY) gained) of oral bisphosphonates*




Data from [4]. Using a simulation model, this study [4] estimated the lifetime effectiveness per patient for real-world and full adherence with oral bisphosphonate compared with no treatment. Analysis was conducted in Belgian patients aged 55 to 85 years either with a bone mineral density T-score ≤ -2.5 or a prevalent vertebral fracture at baseline.

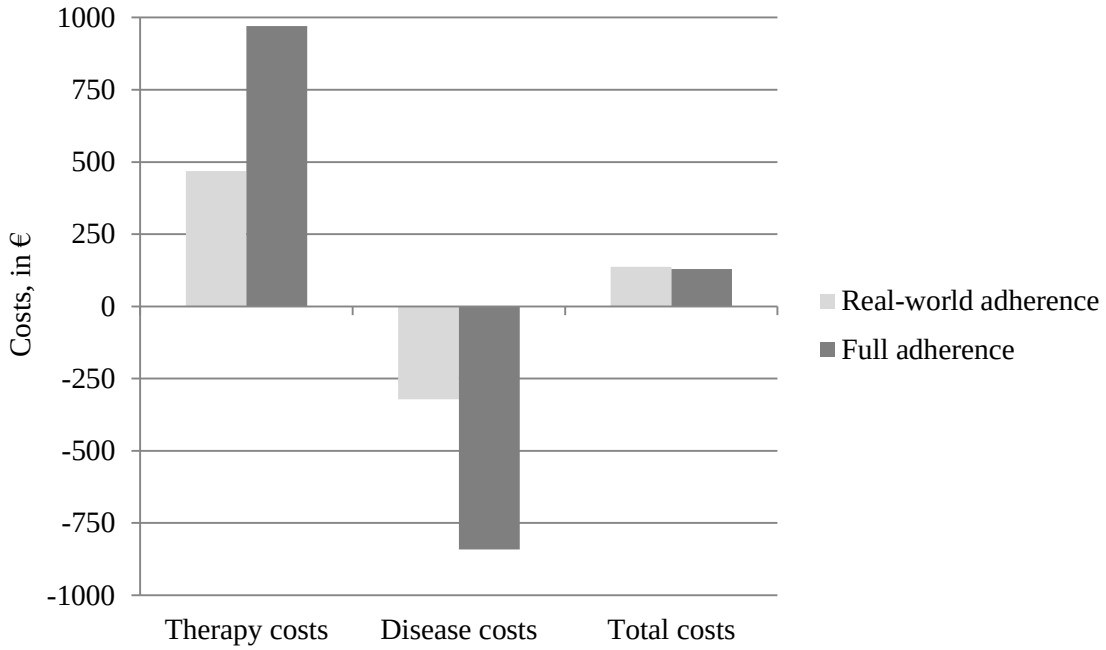
## IMPACT OF POOR ADHERENCE ON HEALTHCARE COSTS

Poor adherence will work in two opposite directions on healthcare resources [1]. Non-adherence reduces the cost of therapy but increases healthcare costs associated with the condition being treated as a result of reducing clinical effectiveness. The final impact of non-adherence on healthcare costs will be primarily dependent on the risk of the population. The impact of poor adherence on therapy cost will be the same across different populations but the number of fractures avoided and the

corresponding disease-related costs are increasing as the fracture risk of the population increases. It could therefore be possible, in high risk populations, that the averted costs of treating the additional osteoporotic fractures resulting from non-compliance will exceed the cost of the additional therapy stemming from the improved compliance.

In our example including women aged between 55 and 85 years with either a bone mineral density (BMD) T-score below -2.5 or a prevalent vertebral fracture, the full and the real-world adherence scenarios had approximately the same total cost [4] (Figure 2), meaning that the additional costs from treating non-adherent patients to full adherence are around equal to the averted fracture costs resulting from improved adherence. Of course, the change in drug and nondrug costs is function of both persistence and compliance [1, 28].

**Figure 2**| *Impact of medication non-adherence on aggregated and disaggregated (drug and disease) healthcare costs*



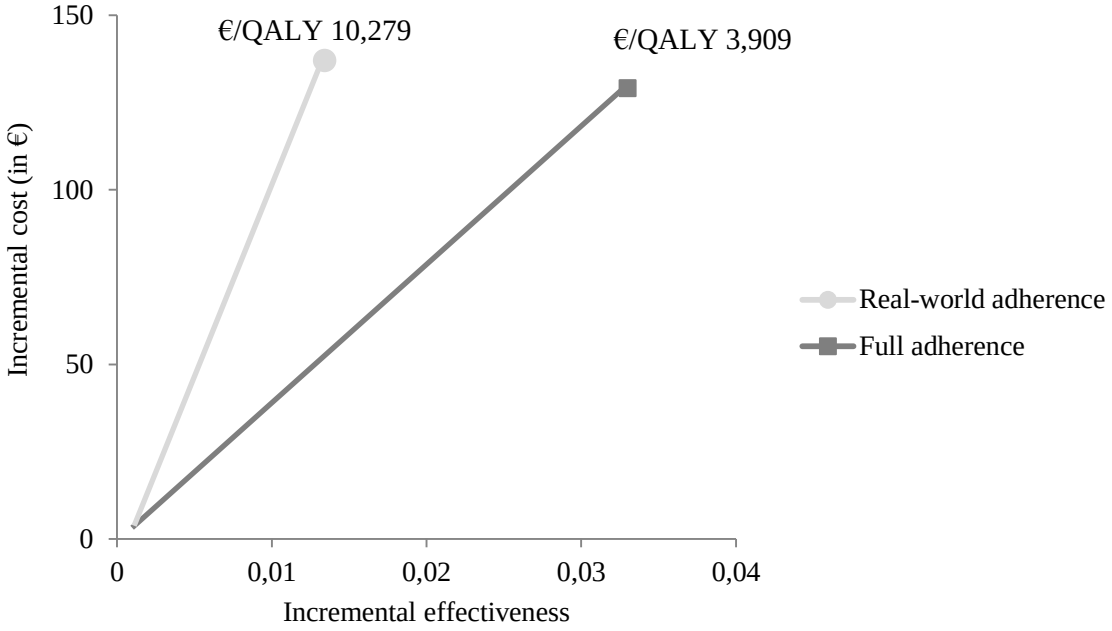

*Data from [4]. Using a simulation model, this study [4] estimated the aggregated and disaggregated costs associated with oral bisphosphonate therapy at real-world adherence and full adherence levels, in comparison with no treatment. Analysis was conducted in Belgian patients aged 55 to 85 years either with a bone mineral density T-score ≤ -2.5 or a prevalent vertebral fracture at baseline. Aggregated costs (total costs) include the costs of therapy (drug and monitoring costs) and fracture-related costs (disease costs).*

## IMPACT OF POOR ADHERENCE ON COST-EFFECTIVENESS

Given that compliance and persistence affect both health outcomes and costs, these concepts should be included to accurately estimate the cost-effectiveness of drug therapies. In our example using observational data (Figure 3), the impact of medication adherence on the cost-effectiveness is substantial. The incremental cost per QALY gained of oral bisphosphonates compared with no treatment was estimated at €10,279 and €3,909 at real-world and full (assumed) adherence levels,

respectively [4]. Poor adherence therefore results in this example in around a doubling of the cost-effectiveness from these medications. It means that for example, with a budget of €20,000, treatment with oral bisphosphonate could save 1.95 life-years in perfect health at real-world adherence levels while, at full adherence, treatment could prevent 5.12 life-years in perfect health. The studies addressing compliance and persistence have shown that both aspects of adherence were important drivers of cost-effectiveness [5].

**Figure 3|** *Impact of medication non-adherence on the cost-effectiveness (expressed as cost in € per QALY gained) of oral bisphosphonates compared with no treatment.*




*Data from [4]. This figure (called the 'cost-effectiveness plane') presents the incremental effectiveness and costs of oral bisphosphonates compared with no treatment at real-world and full adherence levels. The incremental cost-effectiveness ratio is represented by the slope of the line from the origin. The analysis was conducted in Belgian patients aged 55 to 85 years either with a bone mineral density T-score ≤ -2.5 or a prevalent vertebral fracture at baseline.*

## APPROACHES TO INTEGRATE NON-PERSISTENCE AND NON-COMPLIANCE IN ECONOMIC EVALUATIONS

Over the recent years, several studies have attempted to integrate medication compliance and/or persistence in pharmacoeconomic evaluations conducted in osteoporosis. As compliance and persistence are two different constructs, both concepts should be ideally separated. In order to not blur the distinction between compliance and persistence, it is also important that compliance was defined in the subgroup of persistent patients. Studies generally provide assumptions with respect to persistence but generally oversimplify the contribution of compliance. We describe below some of the approaches to integrate persistence and compliance.

In the first economic models of persistence, including one by the National Institute for Health and Clinical Excellence in the United Kingdom, it was assumed that some patients completed the full 5-year course and the remaining (i.e. non-persistent patients) received no treatment effect but 3 months of costs [29, 30]. A value of 50% non-persistent patients was selected in the base-case. Patients who early discontinue therapy may have a marked impact on the cost-effectiveness as they receive drug cost but have no treatment effect. As example, the incremental cost-effectiveness ratio (ICER) of generic alendronate in UK women with bone mineral density T-score equal to -2.5 and no prior fracture was estimated at €3,163, €3,709 and €4,914 per QALY gained when assuming 30%, 50% and 70% of non-persistent patients, respectively [29]. Patients are however likely, in real-life settings, to discontinue at any time and not only after 3 months [30].

More recent studies have therefore added that patients can be at risk of discontinuation over the whole period of time [30-32]. Every patient had therefore in every cycle a risk of stopping therapy, based on observational adherence studies. For patients stopping therapy in each cycle, it is frequently assumed, first, that they receive no further treatment during the remaining modeling time and, secondly, that offset time (i.e. effect of treatment after stopping therapy) is similar to the duration on therapy. Although the last seems reasonable, assumptions made regarding the offset time may have a large impact on the results [30]. Limited data available from extension studies of RCTs have suggested the discontinuation of oral bisphosphonate resulted in the gradual loss of its effects [33] and found up to 7 years after treatment withdrawal [34]. Further research would however be needed to understand offset action of new anti-osteoporosis medications. The first assumption may be more critical as around one third of patients were shown to restart treatment within 6 months after discontinuation [35, 36]. How these patients change the cost-effectiveness is however unclear, and their inclusion in modeling may be difficult as the effectiveness of oral bisphosphonates used in an interrupted way is largely unknown.

Studies have also attempted to include medication compliance. Most studies assumed medication costs and fracture reduction efficacy to be proportional to compliance [27, 37, 38]. This approach may however be inappropriate since the relationship between MPR and fracture risk has been shown in most studies to be nonlinear [11].

Ström et al. (2009) used another approach to model compliance. They reduced treatment efficacy by a proportional factor of the optimal anti-fracture effect [30]. The authors suggested a 20% reduction of treatment benefit due to non-compliance in the base-case, based on experts' opinion. Non-compliant patients therefore deteriorated the cost-effectiveness because they received less benefit but the same cost.

Hiligsmann et al. (2010) estimated the relative risks of fracture according to MPR [5]. The effectiveness from clinical trials was applicable to the population with an MPR value equal to 80% and fracture reduction efficacy at other MPR values was estimated based on the relationship

between compliance and fracture risk [19, 21]. For generic oral bisphosphonates, the incremental cost-effectiveness ratio was estimated at €4,871, €11,985, and €30,181 for 100%, 80%, and 60% compliance, respectively.

Hiligsmann et al. suggest an original methodology including real-world estimates for compliance with oral bisphosphonates [4, 8, 34]. Persistent patients were classified as compliant (MPR ≥80%) and poorly compliant (MPR <80%). The probabilities of being compliant or not were derived for any given year and poorly compliant patients were assumed to be associated with an increased risk of fractures [21, 39]. Drug costs were also related to the mean MPR of the patients.

Using this approach, the cost-effectiveness of denosumab compared with generic alendronate (an oral bisphosphonate) was estimated in the treatment of postmenopausal osteoporotic women [32], using real-world adherence data for alendronate and accepting an improved persistence for the 6-month subcutaneous injection of denosumab based on the results of an open-label study [40]. A shorter offset time of the anti-fracture effect after stopping treatment was assumed for denosumab as compared to the one selected for alendronate. In the base-case analysis, the cost per QALY gained of denosumab compared with generic alendronate was estimated at €22,220 in women aged 70 years with bone mineral density T-score of -2.5 or less. When assuming a 25% higher adherence for oral bisphosphonates, the ICER increased to €41,759. Medication adherence can therefore be considered as a key driver of the results. If adherence would have not been included, the ICER of denosumab compared to oral bisphosphonates would be less favorable. When comparing drugs with potential differences in medication compliance and persistence, the lack of inclusion of these concepts could bias the results and lead to suboptimal allocation of resources.

## ECONOMIC VALUE OF ADHERENCE-ENHANCING INTERVENTIONS

Over the recent years, there has been an increasing interest to determine the effects of programs to improve adherence with osteoporosis medications. Several studies have investigated the effects of changing the dosing of regimens of bisphosphonates and/or improvements of compliance and persistence on the number of fractures prevented [6, 41-44]. Some studies also estimated the economic value (in terms of cost per QALY gained) of improving medication compliance and persistence [26, 30, 45]. These studies did not assess the cost-effectiveness of a specific program but estimated the cost-effectiveness of hypothetical interventions. As mentioned above, depending on the baseline risk for fractures such interventions can, but will not necessarily be cost-effective.

Results of these studies suggest that interventions to improve adherence may likely confer cost-effectiveness benefits. So, for example, a hypothetical intervention with a one-time cost of $250 and reducing discontinuation by 30% had an incremental cost per QALY gained of $29,571 in American women aged 65 years starting bisphosphonates [26]. Other studies [4, 31, 47], reported in Table 1, estimated the maximum amount per year it would be cost-effective to spend on

interventions to improve medication adherence, depending on the level of improvement (between 10% and 50%).

**Table 1|** *Maximum cost per year for an adherence-enhancing intervention to be considered as cost-effective*

| Adherence improvement by | Sweden, 2009* [30] | Belgium, 2010** [4] | Ireland, 2012** [45] |
|---|---|---|---|
| 10% | €225 | €73 | €119 |
| 25% (30% for Sweden ) | €676 | €149 | €299 |
| 50% | €1130 | €239 | €726 |

** Cost-effectiveness threshold of €60,000 per QALY gained. ** Cost-effectiveness threshold of €45,000 per QALY gained.*

## CHALLENGES FOR INTEGRATING COMPLIANCE AND PERSISTENCE IN PHARMACOECONOMIC EVALUATIONS

Medication persistence and compliance are important drivers of cost-effectiveness analyses conducted in osteoporosis and should therefore be incorporated in pharmacoeconomic analyses. Measuring adherence and incorporating it into health economic modeling may, however, pose particular challenges. A number of avenues for further research have recently been identified [13].

First, it is probably needed to have better (and standardized) definition for compliance thresholds and for gap lengths for non-persistence. This is particularly important for new osteoporotic treatments with different dosing regimens. Persistence data seems to be highly sensitive to gap length which remains especially uncertain for longer dosing regimens. Improvements in the measurement of compliance and persistence are also required. The development and validation of tools to evaluate adherence (including missing doses and wrong timing) to osteoporosis medications would be useful [46]. Patient-related outcomes from validated questionnaires may provide robust complementary alternatives to medico-administrative database analyses, and especially for compliance measurement.

Second, given the large difference between efficacy and effectiveness, improvements in the collection of data, preferably in real-life setting, are expected. Using local and treatment-specific data are also important. Currently, the majority of studies have considered the effect of adherence to oral bisphosphonate therapies. Further work are expected to assess compliance and persistence with recent osteoporosis medications with longer dosing regimens. There is also a need to conduct studies to assess efficacy and effectiveness according to types and levels of compliance. Retrieving efficacy data from RCTs for high compliance, as currently frequently done, may be incorrect because compliance in the trials is not optimal for all the patients. The efficacy from these trials is likely to be reduced to some degree because of non-compliance and non-persistence. Therefore, using efficacy data from RCT for high compliance probably underestimates the true underlying risk

reduction with therapy. Clinical results should therefore also be related to the doses taken and not an assumed 100% persistence and compliance [47]. Although compliance and persistence should be better reported in clinical trials, data on compliance and relation to effectiveness would ideally be derived from register/observational studies. Additional insight into variables associated with non-compliance (such as age, first or second fracture, multi-medication or comorbidity) would also be valuable. Many factors (such as the presence of comorbidities) are associated with medication adherence [48] and may therefore have an impact on the economic consequences of non-adherence. The effect of these factors should be further investigated.

Finally, parallel with improvements in the collection of data, further work on the methods to incorporate medication compliance and persistence in economic evaluations are also required. This should consider the inclusion of patients who restart therapy after discontinuation and better estimates of the true cost for compliant and non-compliant patients. Using microsimulation models, it would also be possible to integrate an impact of events (such as prior fractures, discontinuation) on compliance and persistence. Modeling compliance and persistence as continuous variables rather than as dichotomous could also improve the power of the analysis. It is also recommended to perform sensitivity analyses on adherence data and assumptions.

## EXPERT COMMENTARY

Ten years ago, Hughes et al. [49] and Cleemput et al. [50] reviewed the literature on the economic impact of non-compliance and identified a need for more and better research. In 2007 and 2009, Hughes et al. [1] and Rosen et al. [51] provided an update of the reviews suggesting that the work is still sparse, and that the limited evidence available has methodological limitations.

In osteoporosis, the incorporation of medication compliance and persistence in pharmacoeconomic evaluations is relatively recent. Most studies recognize the importance of incorporating adherence in health economic models in osteoporosis [5, 13, 30]. Despite this, these concepts are not yet routinely included. Moreover, when adherence was included, a lack of methodological rigor and consistency in definitions may reduce the impact of medication non-adherence. Few studies have included both persistence and compliance aspects of treatment adherence. It should however be noted that substantial improvements have been made in some recent studies. As discussed in this paper, the incorporation of medication compliance and persistence in pharmacoeconomic evaluations may be difficult and challenging, also depending on data availabilities. Further research is required and should include the development of appropriate methodology and standards [1].

The importance of integrating medication compliance and persistence in pharmacoeconomic analyses is evident in osteoporosis, but this extends beyond this disease area. Previous studies have shown that non-compliance and non-persistence have substantial economic impact in patients with hypertension [52], with diabetes mellitus [53, 54] or with renal transplantation [55]. Health

economic modelers should therefore consider the possible impact of non-adherence in all economic evaluations of drug or lifestyle interventions.

## FIVE-YEAR VIEW

Medication compliance and persistence represents a new perspective on health technology assessment in osteoporosis [13]. It is our beliefs that, over the next five years, there will an increase in the health economic papers incorporating medication compliance and persistence. This will be in line with the collection of additional adherence data. Moreover, as strategies to improve compliance and persistence may confer clinical and cost-effectiveness benefits, we would expect research on the effectiveness and cost-effectiveness of such programs.

## KEY ISSUES

- Medication non-compliance and non-persistence reduces treatment effectiveness, impact on healthcare costs and may therefore alter the cost-effectiveness of drug therapies
- A few studies carried out to date have suggested important economic implications of poor compliance and persistence with osteoporosis medications.
- Compliance and persistence should be an integral part of clinical (observational) studies and pharmacoeconomic analyses in order to estimate the cost-effectiveness of drug therapies in the current community practice.
- Including adherence and incorporating it into health economic modeling may be difficult challenging.
- Depending on their cost and effects, interventions to improve compliance and persistence with osteoporosis medications may confer cost-effective benefits.
- The cost-effectiveness of specific adherence-enhancing interventions should be explored.

## REFERENCES


1. Hughes D, Cowell W, Koncz T, Cramer J. Methods for integrating medication compliance and persistence in pharmacoeconomic evaluations. Value Health. 2007;10(6):498-509.
2. Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int. 2006;17(11):1645-52.
3. Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc. 2007;82(12):1493-501.
4. Hiligsmann M, Rabenda V, Bruyere O, Reginster JY. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy. 2010;96(2):170-7.
5. Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY. Potential Clinical and Economic Impact of Nonadherence with Osteoporosis Medications. Calcif Tissue Int. 2010;86(3):202-10.
6. Danese MD, Badamgarav E, Bauer DC. Effect of adherence on lifetime fractures in osteoporotic women treated with daily and weekly bisphosphonates. J Bone Miner Res. 2009;24(11):1819-26.
7. Landfeldt E, Lundkvist J, Strom O. The societal burden of poor persistence to treatment of osteoporosis in Sweden. Bone. 2011;48(2):380-8.
8. Hiligsmann M, Gathon HJ, Bruyere O, Ethgen O, Rabenda V, Reginster JY. Cost-Effectiveness of Osteoporosis Screening Followed by Treatment: The Impact of Medication Adherence. Value Health. 2010;13:394-401.
9. Lekkerkerker F, Kanis JA, Alsayed N, Bouvenot G, Burlet N, Cahall D, et al. Adherence to treatment of osteoporosis: a need for study. Osteoporos Int. 2007;18(10):1311-7.
10. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11(1):44-7.
11. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RMC, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med. 2009;122(2 Suppl):S3-13.
12. Cotte FE, Mercier F, De Pouvourville G. Relationship between compliance and persistence with osteoporosis medications and fracture risk in primary health care in France: a retrospective case-control analysis. Clin Ther. 2008;30(12):2410-22.
13. Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. Osteoporos Int. 2011; 22(10):2565-73
14. Gold DT. Medication adherence: a challenge for patients with postmenopausal osteoporosis and other chronic illnesses. J Manag Care Pharm. 2006;12(6 Suppl A):S20-5; quiz S6-8.
15. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther. 2001;26(5):331-42.
16. Rabenda V, Reginster JY. Overcoming problems with adherence to osteoporosis medication. Expert Rev Pharmacoecon Outcomes Res. 2010;10(6):677-89.
17. Ross S, Samuels E, Gairy K, Iqbal S, Badamgarav E, Siris E. A meta-analysis of osteoporotic fracture risk with medication nonadherence. Value Health. 2011;14(4):571-81.
18. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int. 2010;21(11):1943-51.

19. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc. 2006;81(8):1013-22.
20. Briesacher BA, Andrade SE, Yood RA, Kahler KH. Consequences of poor compliance with bisphosphonates. Bone. 2007;41(5):882-7.
21. Rabenda V, Mertens R, Fabri V, Vanoverloop J, Sumkay F, Vannecke C, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int. 2008;19(6):811-8.
22. Landfeldt E, Strom O, Robbins S, Borgstrom F. Adherence to treatment of primary osteoporosis and its association to fractures-the Swedish Adherence Register Analysis (SARA). Osteoporos Int. 2012;23(2):433-43.
23. Gallagher AM, Rietbrock S, Olson M, van Staa TP. Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res. 2008;23(10):1569-75.
24. Curtis JR, Larson JC, Delzell E, Brookhart MA, Cadarette SM, Chlebowski R, et al. Placebo adherence, clinical outcomes, and mortality in the women's health initiative randomized hormone therapy trials. Med Care. 2011;49(5):427-35.
25. Cadarette SM, Solomon DH, Katz JN, Patrick AR, Brookhart MA. Adherence to osteoporosis drugs and fracture prevention: no evidence of healthy adherer bias in a frail cohort of seniors. Osteoporos Int 2011;22(3):943-54.
26. Patrick AR, Schousboe JT, Losina E, Solomon DH. The Economics of Improving Medication Adherence in Osteoporosis: Validation and Application of a Simulation Model. J Clin Endocrinol Metab. 2011; 96(9):2762-70.
27. Hiligsmann M, Ethgen O, Bruyere O, Richy F, Gathon HJ, Reginster JY. Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. Value Health. 2009;12(5):687-96.
28. Cotte FE, De Pouvourville G. Cost of non-persistence with oral bisphosphonates in post-menopausal osteoporosis treatment in France. BMC Health Serv Res. 2011;11:151.
29. Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. Bone. 2008;42(1):4-15.
30. Strom O, Borgstrom F, Kanis JA, Jonsson B. Incorporating adherence into health economic modelling of osteoporosis. Osteoporos Int. 2009;20(1):23-34.
31. Jonsson B, Strom O, Eisman JA, Papaioannou A, Siris ES, Tosteson A, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. Osteoporos Int. 2011;22(3):967-82.
32. Hiligsmann M, Reginster JY. Cost Effectiveness of Denosumab Compared with Oral Bisphosphonates in the Treatment of Post-Menopausal Osteoporotic Women in Belgium. Pharmacoeconomics. 2011; 29(10):895-911.
33. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004;350(12):1189-99.
34. Bagger YZ, Tanko LB, Alexandersen P, Ravn P, Christiansen C. Alendronate has a residual effect on bone mass in postmenopausal Danish women up to 7 years after treatment withdrawal. Bone. 2003;33(3):301-7.
35. Lo JC, Pressman AR, Omar MA, Ettinger B. Persistence with weekly alendronate therapy among postmenopausal women. Osteoporos Int. 2006;17(6):922-8.

36. Brookhart MA, Avorn J, Katz JN, Finkelstein JS, Arnold M, Polinski JM, et al. Gaps in treatment among users of osteoporosis medications: the dynamics of noncompliance. Am J Med. 2007;120(3):251-6.
37. Schousboe JT, Taylor BC, Fink HA, Kane RL, Cummings SR, Orwoll ES, et al. Cost-effectiveness of bone densitometry followed by treatment of osteoporosis in older men. JAMA. 2007;298(6):629-37.
38. Mueller D, Weyler E, Gandjour A. Cost effectiveness of the German screen-and-treat strategy for postmenopausal osteoporosis. Pharmacoeconomics. 2008;26(6):513-36.
39. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006;38(6):922-8.
40. Kendler DL, Bessette L, Hill CD, Gold DT, Horne R, Varon SF, et al. Preference and satisfaction with a 6-month subcutaneous injection versus a weekly tablet for treatment of low bone mass. Osteoporos Int. 2010;21(5):837-46.
41. Cotte FE, Cortet B, Lafuma A, Avouac B, Hasnaoui AE, Fardellone P, et al. A model of the public health impact of improved treatment persistence in post-menopausal osteoporosis in France. Joint Bone Spine. 2008;75(2):201-8.
42. Cotte FE, Fautrel B, De Pouvourville G. A Markov model simulation of the impact of treatment persistence in postmenopausal osteoporosis. Med Decis Making. 2009;29(1):125-39.
43. Earnshaw SR, Graham CN, Ettinger B, Amonkar MM, Lynch NO, Middelhoven H. Cost-effectiveness of bisphosphonate therapies for women with postmenopausal osteoporosis: implications of improved persistence with less frequently administered oral bisphosphonates. Curr Med Res Opin. 2007;23(10):2517-29.
44. Rietbrock S, Olson M, van Staa TP. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. QJM. 2009;102(1):35-42.
45. Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. Value Health 2012;15(5):604-12.
46. Breuil V, Cortet B, Cotte FE, Arnould B, Dias-Barbosa C, Gaudin AF, et al. Validation of the adherence evaluation of osteoporosis treatment (ADEOS) questionnaire for osteoporotic post-menopausal women. Osteoporos Int. 2012;23(2):445-55.
47. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336(7653):1114-7.
48. Papaioannou A, Kennedy CC, Dolovich L, Lau E, Adachi JD. Patient adherence to osteoporosis medications: problems, consequences and management strategies. Drugs Aging. 2007;24(1):37-55.
49. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. Health Econ. 2001;10(7):601-15.
50. Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the economics of noncompliance. Room for methodological improvement. Health Policy. 2002;59(1):65-94.
51. Rosen AB, Spaulding AB, Greenberg D, Palmer JA, Neumann PJ. Patient adherence: a blind spot in cost-effectiveness analyses? Am J Manag Care. 2009;15(9):626-32.

52. Cherry SB, Benner JS, Hussein MA, Tang SS, Nichol MB. The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. Value Health. 2009;12(4):489-97.
53. Breitscheidel L, Stamenitis S, Dippel FW, Schoffski O. Economic impact of compliance to treatment with antidiabetes medication in type 2 diabetes mellitus: a review paper. J Med Economics. 2010;13(1):8-15.
54. Salas M, Hughes D, Zuluaga A, Vardeva K, Lebmeier M. Costs of medication nonadherence in patients with diabetes mellitus: a systematic review and critical analysis of the literature. Value Health. 2009;12(6):915-22.
55. Cleemput I, Kesteloot K, Vanrenterghem Y, De Geest S. The economic implications of non-adherence after renal transplantation. Pharmacoeconomics. 2004;22(18):1217-34.

# PART 2

## ADHERENCE STUDIES

CHAPTER 6

# THE CLINICAL AND ECONOMIC BURDEN OF POOR ADHERENCE AND PERSISTENCE WITH OSTEOPOROSIS MEDICATIONS IN IRELAND

**Hiligsmann M**, McGowan, Bennett K, Barry M, Reginster JY

*Value in Health, 2012, 15(5), 604-12*

## ABSTRACT

*OBJECTIVES:* Medication non-adherence is common for osteoporosis, but the consequences have not been well described. This study aims to quantify the clinical and economic impacts of poor adherence and to evaluate the potential cost-effectiveness of improving patient adherence using hypothetical behavioral interventions.

*METHODS:* A previously validated Markov microsimulation model was adapted to the Irish setting to estimate lifetime costs and outcomes (fractures and quality-adjusted life-year (QALY)) for three adherence scenarios: no treatment, real-world adherence and full adherence over 3 years. The real-world scenario employed adherence and persistence data from the Irish HSE-PCRS pharmacy claims database. We also investigated the cost-effectiveness of hypothetical behavioral interventions to improve medication adherence (according to their cost and effect on adherence).

*RESULTS:* The number of fractures prevented and the QALY gain obtained at real-world adherence levels represented only 57% and 56% of those expected with full adherence, respectively. The costs per QALY gained of real-world adherence and of full adherence compared with no treatment were estimated at €11,834 and €6,341. An intervention to improve adherence by 25% would result in an ICER of €11,511/QALY and €54,182/QALY, compared with real-world adherence, if the intervention cost an additional €50 and €100 per year, respectively.

*DISCUSSION:* Poor adherence with osteoporosis medications results in around a 50% reduction in the potential benefits observed in clinical trials and a doubling of the cost per QALY gained from these medications. Depending on their costs and outcomes, programs to improve adherence have the potential to be an efficient use of resources.



## KEYWORDS

Medication adherence, medication persistence, osteoporosis, intervention, cost-effectiveness.

## INTRODUCTION

The management of osteoporosis is becoming a major priority in public health. At least one in three women over 50 years of age, and one in five men, will suffer an osteoporotic fracture in their remaining lifetime [1]. These fractures result in significant morbidity and mortality, reduction in quality of life and pose considerable costs to already stretched health care systems [2, 3]. Figures derived from the International Osteoporosis Foundation estimate that approximately 300,000 people over the age of 50 years have osteoporosis in Ireland. This figure represents 25% of this population. The results of an Irish Burden of Illness Study demonstrated that fall related injuries in the elderly cost the Irish Health care system approximately €402 million each year [4]. With an increasingly elderly population and longer life expectancy the burden is set to increase.

Fortunately, an increasing number of pharmacological agents have become available in the last ten years for the treatment of low bone mineral density. Numerous clinical trials and meta-analyses have shown that anti-osteoporosis medications and in particular the oral bisphosphonates significantly reduce the risk of both vertebral and non-vertebral fractures [5]. In addition, economic analyses, typically based on efficacy estimates drawn from clinical trials, have consistency shown these medications to be cost-effective in a wide range of patient profiles for both primary and secondary prevention [6, 7].

Despite the availability of proven effective pharmacotherapy for managing osteoporosis, studies are continuing to show that post fracture treatment with anti-osteoporotic medications remains suboptimal [8, 9]. Furthermore in more recent years the issue of non-adherence with drug therapy particularly in chronic asymptomatic diseases such as osteoporosis further compromises the clinical and economic effects of the management of these patients. Adherence to treatments in patients with osteoporosis has been found to be suboptimal in several studies [10-12]. These studies have concluded that between 50-75% of patients who were initiated anti-osteoporotic medications have discontinued their medications within 12 months of commencement. Although it is well recognized that poor adherence reduces the potential benefits of osteoporosis therapy, lowering gains in bone mineral density resulting in increased risk of fragility fractures [13], the clinical and economic consequences at a population level have been rarely studied [14, 15]. A few studies carried out to date have however suggested potential important clinical and/or economic implications of poor adherence to osteoporosis medications [16-19].

Adherence is influenced by health beliefs such as risk perception, perceived benefits and disadvantages of drugs, self-efficacy, as well as stage of change and communication problems with physicians [20]. Over recent years, behavioral interventions to improve patient adherence have been developed [21, 22]. Although their effectiveness still require further validation, educational programmes and patient counselling by nurses may be effective in improving patient adherence.

New therapeutic options with longer dosing regimens have also been recently available for the prevention and treatment of osteoporosis that may, at least in principle, further help to increase adherence. Under limited resources, it is becoming increasingly important to examine how cost-effective an intervention should be in order for it to be considered worthwhile. Using simulation modelling, which allowed us to capture the long-term effects of medications, this study aims to quantify the clinical and economic effects of poor adherence with osteoporosis medications in Ireland and to estimate the potential cost-effectiveness of hypothetical interventions to improve medication adherence according to their cost and effect on adherence.

## METHODS

A published and validated Markov microsimulation model on the natural history of osteoporosis was developed by Hiligsmann et al. (2009) [23] and has been frequently used to assess the cost-effectiveness of osteoporosis management in Belgium [18, 24-28]. The model was recently updated with a 6-month cycle length to estimate the cost-effectiveness of denosumab [28]. We used this updated model to assess the clinical and economic burden of poor adherence from the Irish public healthcare perspective, i.e. the Health Services Executive (HSE). The model was programmed using the software TreeAge Pro 2011 (TreeAge Pro Inc., Williamston, MA, USA).

The simulation model estimated fracture events, costs and quality-adjusted life years (QALYs) for three adherence scenarios: no treatment, real-world adherence and full adherence. The 'no treatment' scenario included no costs and no benefits of treatment. The real-world scenario employed adherence and persistence data from the Irish Health Services Executive-Primary Care Reimbursement Services (HSE-PCRS) pharmacy claims database for all treatment-naïve patients over the age of 55 years who started osteoporosis medications in Ireland between 2006 and 2009 and the full adherence scenario assumed that patients were fully adherent over 3 years. Patients therefore received treatment in the model for a maximum of 3 years, because most clinical trials last only three years and adherence data were collected over this period. However, the model simulated a patient's lifetime (that is, until death or 100 years) in order to capture all relevant costs and consequences of fractures experienced during treatment period.

A description of the different components of the model is outlined in this section. Most model data are included in Table 1. More details can be found on Appendix 1. Please also refer to previously published research [17, 23] for limitations of the model and an illustration on how the model integrates memory [23].

**Table 1**| *Fracture incidence, costs, excess mortality and utility values used in the model*

| Parameter | Women | Men | Reference |
|---|---|---|---|
| **Incidence (annual rate/1000 persons-years)** | | | |
| Hip fracture | 1.12 (60-64 y), 1.99 (65-69 y), 4.73 (70-74 y), 9.80 (75-79 y), 17.47 (80-84 y), 32.97 (+85 y) | 0.62 (60-64 y), 1.51 (65-69 y), 2.02 (70-74 y), 5.68 (75-79 y), 10.69 (80-84 y), 20.01 (+85 y) | Health Atlas Ireland |
| CV fracture | 1.75 (60-64 y), 2.81 (65-69 y), 6.67 (70-74 y), 8.32 (75-79 y), 9.42 (80-84 y), 14.63 (+85 y) | 1.97 (60-64 y), 1.81 (65-69 y), 3.38 (70-74 y), 5.61 (75-79 y), 6.56 (80-84 y), 14.13 (+85 y) | [1] |
| Wrist fracture | 3.28 (60-64 y), 4.42 (65-69 y), 7.75 (70-74 y), 7.73 (75-79 y), 9.78 (80-84 y), 12.36 (+85 y) | 1.22 (60-64 y), 2.11 (65-69 y), 0.60 (70-74 y), 1.59 (75-79 y), 1.82 (80-84 y), 3.82 (+85 y) | [1] |
| Other fracture* | 2.55 (60-64 y), 4.98 (65-69 y), 6.77 (70-74 y), 13.07 (75-79 y), 15.40 (80-84 y), 35.10 (+85 y) | 2.31 (60-64 y), 5.56 (65-69 y), 5.18 (70-74 y), 6.91 (75-79 y), 22.47 (80-84 y), 28.67 (+85 y) | [1] |
| **Relative risk of fracture attributable to osteoporosis** | | | |
| Hip fracture | 3.39 (60-69 y), 2.25 (70-79 y), 1.57 (+80 y) | 4.76 (60-69 y), 3.58 (70-79 y), 2.05 (+80 y) | [29] |
| CV fracture | 2.18 (60-69 y), 1.77 (70-79 y), 1.51 (+80 y) | 2.65 (60-69 y), 2.39 (70-79 y), 1.93 (+80 y) | [29] |
| Wrist fracture | 1.61 (60-69 y), 1.43 (70-79 y), 1.30 (+80 y) | 1.81 (60-69 y), 1.70 (70-79 y), 1.50 (+80 y) | [29] |
| Other fracture | 1.90 (60-69 y), 1.61 (70-79 y), 1.42 (+80 y) | 2.23 (60-69 y), 2.05 (70-79 y), 1.73 (+80 y) | [29] |
| **Excess mortality after hip and clinical vertebral fracture** | | | |
| 0-6 m, 6-12 m , subs y | 4.53, 1.75, 1.78 | 5.75, 2.31, 1.69 | [32] |
| **Direct fracture costs (in €2008)** | | | |
| Hip, 1st 6-month | From 11,215 to 13,140 | From 12,053 to 14,042 | Health Atlas Ireland |
| Hip, yearly long-term costs | From 4,449 to 4,805 | From 4,523 to 4,845 | HSE and [35] |
| CV, 1st 6-month | From 1,950 to 2,285 | From 2,096 to 2,442 | [36] |
| Wrist, 1st 6-month | From 1,624 to 1,903 | From 1,746 to 2,034 | [36] |
| Other, 1st 6-month | From 1,947 to 2,281 | From 2,093 to 2,438 | [36] |

| **Health states utility values** | | | |
|---|---|---|---|
| General population | 0.83 (60-69 y), 0.77 (70-79 y), 0.72 (+80 y) | 0.84 (60-69 y), 0.78 (70-79 y), 0.71 (+80 y) | [37] |
| Hip (1st y / subs. y)** | | 0.80 / 0.90 | [37] |
| CV (1st y / subs. y)** | | 0.72 / 0.93 | [37, 53] |
| Wrist (1st y / subs. y)** | | 0.94 / 1.00 | [37, 53] |
| Other (1st y / subs. y)** | | 0.91 / 1.00 | [37] |

*CV: clinical vertebral, M: month, Y: year, Subs: subsequent*

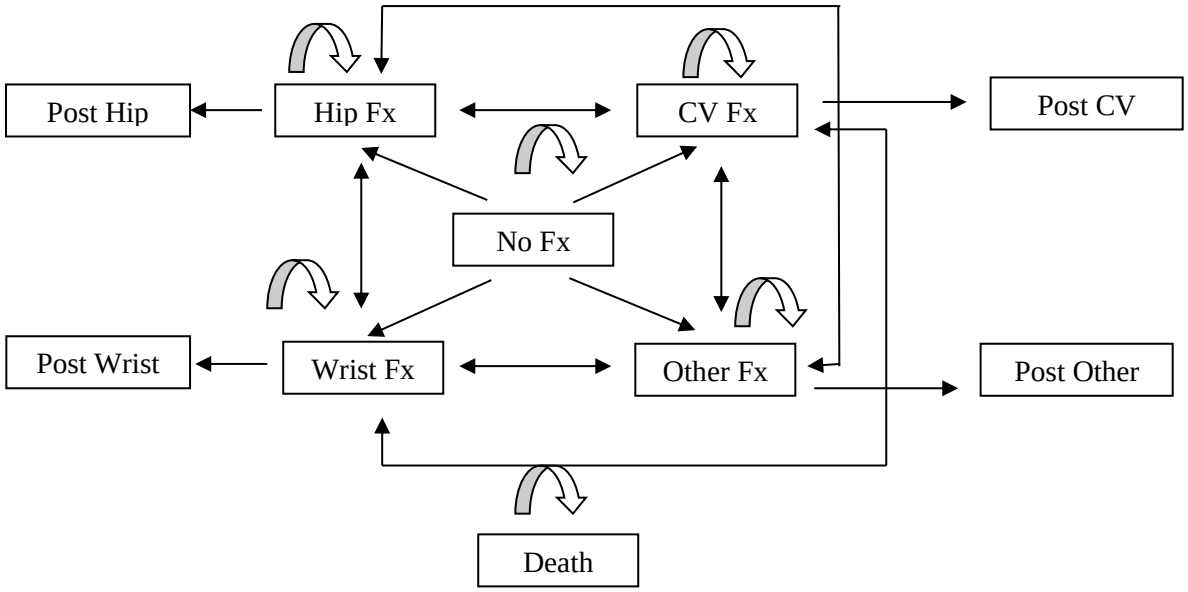
** Other fractures included humerus, tibia/fibula, pelvis and ribs fractures*

******* *Relative reduction in health utility value, represents the proportional loss of QALY due to the fracture*

*MODEL STRUCTURE*

Figure 1 provides an overview of the model. The model health states are no fracture, death, hip fracture, clinical vertebral fracture, wrist fracture, other fracture and the corresponding post-fracture states. Post-fracture states were created as some parameters (e.g. fracture disutility) were estimated over a 1-year period [28]. All the patients, one at a time, began in the 'no fracture' state and had, every 6 months, a probability of having a fracture of the hip, clinical vertebrae, wrist, or other site or dying. Patients in a fracture state can stay in the same fracture state if they re-fracture, change to another fracture state, die or change in the next cycle to the post-fracture state. Patients being in any post-fracture state might have a new fracture (all fracture types are possible), die or move to the 'no fracture' state. Tracker variables were created to record the number of each fracture type and used to adjust transition probabilities, costs and utilities to reflect the impact of prior fractures.

**Figure 1**| *Model structure*




*Transitions to death and from post-fracture states to any fractures states, 'Death' and 'No Fx' were excluded from the graph for simplicity. FX: fracture; CV: clinical vertebral*

*FRACTURE INCIDENCE AND MORTALITY RATES*

Analyses were assessed in patients receiving osteoporosis medications. In Ireland at present, there are no conditions attached for the reimbursement of anti-osteoporosis therapies. Unlike the United Kingdom and other European countries Ireland has access to unlimited prescribing of these products. Therefore clinicians make their decision on whether or not to prescribe these products based on the results of densitometry and bone mineral density (BMD) levels, history of fracture, risk factors, etc. In this study, we assumed that all treated patients have the same risk as patients with osteoporosis, based on the definition of the World Health Organization (i.e. BMD T-score ≤-2.5). All patients were therefore assumed to have the same base-case risk before treatment efficacy is impacted.

In order to accurately reflect the risk of patients with BMD T-score ≤-2.5 in comparison with that of the general population, the risk of fracture in the general population was adjusted by relative risk parameters, using a previously validated method [29] (see Appendix 1 for further details). The incidence of hip fractures in the general population was derived from the Health Atlas Ireland, for year 2008 (http://www.hse.ie/eng/services/maps/). Since the incidence of other fractures was not known, we assumed that the age- and sex-specific ratio of index fracture to hip fracture in Ireland was the same as found in Sweden [1]. This assumption, used in the development of many FRAX® models [30], appears to hold true for West European countries, the USA and Australia [31].

Age-specific mortality rates are available from the Central Statistics office in Ireland and excess mortality was modelled after hip and vertebral fractures [32]. Because excess mortality may be

attributable to comorbidities, we conservatively assumed that only 25% of the excess mortality following a hip or vertebral fracture could be directly or indirectly attributable to the fractures themselves [33, 34].

*FRACTURE COST*

The perspective of the public healthcare payer (i.e. the Health Services Executive) was adopted for all cost estimates. Only direct medical costs were reported. All costs were reported as 2008 values. Direct hip fracture costs are divided into hospitalization cost (in the first cycle following the fracture) and long-term costs for patients being institutionalized following the fracture. The hospitalisation cost of hip fracture was obtained from the Hospital In-Patient Enquiry (HIPE) system for 2008 and the associated Disease Related Group costs, (http://www.healthatlasireland.ie).

The cost of nursing home was selected from the average cost of approved private nursing homes in Dublin North East and Dublin Mid Leinster (N=185) (requested from the Health Services Executive) and the probability of admissions to nursing home after a hip fracture was derived from the study of Berringer et al. (2006) [35]. Of 2034 subjects (men and women) living at home at the time of fracture, 10% were in nursing home care after one year. Because patients might be institutionalized later in life in any case, regardless of their hip fracture, an adjustment was made to only include long-term costs attributable to the fracture itself [23].

Non-hip fractures have been quantified relative to hip fracture on the basis of their costs [36]. So, the costs of wrist, clinical vertebral and other fracture represent 17.4%, 14.5% and 17.4% of the acute hip fracture cost, respectively. Non-hip fractures were conservatively assumed to be not associated with long-term costs.

*FRACTURE DISUTILITY*

Utility values for the general population as well as relative reductions due to fractures in the year following the fracture and in subsequent years were derived from a recent systematic review, which suggested reference values for countries that do not have their own database [37]. The model took into account that the number of fractures is a predictor of quality of life. In the case of an occurrence of a second fracture at the same site, the impact of the first fracture event was reduced by 50%, as previously suggested [23]. For example, if a patient with a prior hip fracture suffered another hip fracture, the relative reduction of utility attributable to the first hip fracture was then 0.95 and the total reduction of utility attributed to both fractures was therefore 0.76 (= 0.95 X 0.80) in the year following the fracture. For an individual with both a hip and vertebral clinical fracture, the total impact on QALY was assumed to be equal to the sum of the impacts related to each of the fractures [26].

*DRUG THERAPY*

Treated patients were assumed to receive the effectiveness of oral bisphoshonates, the most widely prescribed anti-osteoporosis medications in Ireland and worldwide. The clinical effectiveness of oral bisphosphonates in the treatment of women with osteoporosis was derived from a recent meta-analysis conducted for the National Institute for Health and Clinical Excellence (NICE) appraisal and included large randomised controlled trials on alendronate and risedronate [38]. The relative risks of fracture in the treatment group versus the placebo group were 0.71 for hip fracture, 0.58 for clinical vertebral fracture and 0.78 for wrist and other fractures assuming the relative risk for other non-vertebral fracture. The effect of treatment was assumed to linearly decline to zero after stopping therapy, during a duration (called offset-time) equal to the duration of therapy, in line with clinical studies [39]. The mean annual drug cost for patients taking osteoporosis medications in Ireland was estimated at €422.3 for women and at €417.0 for men. The costs of the drugs are taken from the Health Service Executive-Primary Care Reimbursement Services Scheme (HSE-PCRS). In this particular scheme, there is no co-payment for the patients. Monitoring cost includes one yearly physician visit (€65, Health Services Executive, http://www.hse.ie) and one bone densitometry measurement every second year (estimated at €90, Irish Osteoporosis Society, http://www.irishhealth.com/article.html?id=7099). Adverse events were not included in the analysis since randomised studies have not shown significant differences between placebo and actively treated patients [5].

*MEDICATION ADHERENCE*

Adherence data were obtained from the Irish HSE-PCRS database formerly the General Medical Services (GMS) Payments Board scheme. This scheme provides free healthcare to approximately 30% of the Irish population (approximately 1.2 million). Eligibility for the scheme is means tested for those under 70 years of age, and is confined to persons who are unable without undue hardship to arrange general practitioner services for themselves and their dependants. Patients registered under this scheme are dispensed all medicines free of charge. From July 2001 – December 2008, the service has been made available to all those over 70 years of age. While the HSE-PCRS population cannot be considered representative of the entire population, as the elderly and the socially disadvantaged are over-represented, it is estimated to account for approximately 70% of all medicines dispensed in primary care. National prescription files were analysed for the years 2006-2009 to identify all prescription items relating to medicines dispensed for the management of osteoporosis (ATC code M05B) in all patients aged 55 years and above. New users of anti-osteoporosis medications were defined as those not receiving any medication for osteoporosis in the previous 12 months. The final adherence database included a total of 70,669 women and 12,613 men with the majority of these aged over 75 years.

Both persistence and adherence to treatment were measured using the pharmacy claims database. Persistence is defined as “the duration of time from initiation to discontinuation of treatment” [40].

Persistence was defined as a dichotomised variable (persistent or not) as to whether a patient continued therapy beyond an elapsed time period. In this study we vary the time periods (i.e. 6 months to 3 years) and a permissible gap of 9 weeks was selected in the base-case as monthly regimens were included in the database. In the subgroup of persistent patients, adherence was calculated as the medication possession ratio (MPR) which is the ratio between the number of days of medication supplied to the number of days in a time interval. Adherence can be dichotomised (adherent or non-adherent) according to the MPR. The conventional approach is to use a cut-off of 0.8 [41], but this was varied in sensitivity analysis. Patients with a MPR greater than or equal to 0.8 were therefore considered to be adherent, in the base-case analysis. The probability of patients restarting therapy one year after stopping was also estimated. All analyses were performed using SAS (v9.1, SAS Institute Inc, Cary USA).

In the model, patients were at risk of discontinuation within 3 years. For patients who stopped taking their therapy, the treatment cost was stopped in the middle of the dropout cycle and the offset-time period started at the same time. For those who discontinued therapy within six months, no treatment effect was received [42], as at least 6 months of treatment is necessary to reduce the risk of fractures [43, 44]. The mean drug cost of these patients, administrated in the first cycle of the model, was specifically estimated at €119.13 for women and at €97.40 for men (HSE-PCRS database). Patients who discontinued therapy can restart therapy after one cycle without treatment. The maximum duration of treatment remains however limited to three years from the start of the simulation.

Poorly adherent patients (MPR <0.8) suffer from a lower treatment efficacy. Poor adherence was associated with a 17% increase in fractures rates (RR=1.17, 95% CI 1.09-1.25) [10]. The relative risks from the NICE meta-analysis were applicable to the population with adherence of 0.8 or greater. So, for instance, if oral bisphosphonates was assumed to reduce the risk of hip fracture by 29%, then adherent patients would experience a 29% reduction in hip fracture while poorly adherent patients would experience only a 17.1% (0.71 X 1.167 = 0.829) reduction in hip fracture. Drug costs in the groups of poorly and highly adherent patients were adjusted by the mean MPR of the group. In the full adherence scenario, drug cost was equal to the MPR of the group of adherent patients (i.e. MPR ≥0.8) (See Appendix 2, Table 3). Adherent patients from the real-world adherence scenario and patients from the full adherence scenarios were therefore associated with the same drug cost.

*ANALYSES AND SIMULATION*

Patients were stratified into groups according to sex (female/male) and age (55–64 years, 65–69 years, 70–74 years, and 75+ years). They entered into the model at the age of 60 years, 67 years, 72 years and 80 years for the different age groups, respectively. First-order Monte-Carlo microsimulations (trials) were performed for each scenario, and fractures, costs, and QALYs were

recorded over 3 years and over a patient's lifetime. A single outcome's value is the sum of the outcomes (i.e. costs and QALYs) from the states traversed by an individual. By simulating patients one by one, a microsimulation model introduces variability between patients that can be reduced by simulating a large number of patients. 200,000 trials were deemed sufficient to guarantee the stability of the results [28]. To enable variability analyses, each model was run 10 times with 200,000 patients.

The potential loss of benefits resulting from poor adherence was first estimated by comparing the outcomes (i.e. number of fractures and QALYs) obtained at real-world adherence levels with those expected with full adherence. The number of fractures resulting from poor adherence in patients from the database was then determined by multiplying the difference between the lifetime number of fractures in the full and real-world adherence scenarios by the number of patients included in the different age and sex groups. The incremental cost-effectiveness ratio (ICER) was calculated between the three adherence scenarios. ICER is defined as the difference in terms of (lifetime) cost between strategies divided by their difference in terms of (lifetime) effectiveness (here measured as QALYs). An ICER represents the incremental cost per one QALY gained. Mean ICER and the 95% confidence interval (CI) were calculated for each analysis. Future costs and health effects (QALYs) were discounted by 4% annually, according to the Irish guideline for cost-effectiveness research [45].

Sensitivity analyses were performed to assess the impact of assumptions on the results. These include changes in fracture risk, cost and disutility, excess mortality and assumptions on medication adherence. In particular, other refill gaps and MPR thresholds were examined. Additional simulations estimated the cost-effectiveness of hypothetical adherence-enhancing interventions according to their cost (marginal and one-time costs) and effect on adherence (improvements between 10% and 50% [21]). As interventions can be associated with marginal (e.g. monitoring) or one-time (e.g. education program) costs, both aspects were investigated.

## RESULTS

### *ADHERENCE DATA*

In women, persistence rates were 64.3%, 52.7% and 45.0% after 1, 2 and 3 years, respectively (Table 2). These values were 60.0%, 41.1% and 29.4% in men. In the subgroup of persistent patients, the probabilities of being highly adherent (MPR $\geq$0.8) were estimated between 82.3% and 93.0%.

**Table 2**| *Persistence and adherence data in Irish women and men**

| Follow-up | 6 month | 1 year | 1.5 years | 2 years | 2.5 years | 3 years |
|---|---|---|---|---|---|---|
| **Women** | | | | | | |
| Non-persistence | 26.2% | 35.7% | 41.9% | 47.3% | 51.9% | 55.0% |
| Poor adherence | 13.1% | 7.7% | 5.9% | 4.7% | 4.1% | 3.5% |
| High adherence | 60.8% | 56.6% | 52.2% | 48.0% | 43.9% | 41.5% |
| N persistent cases | 52,192 | 42,819 | 35,925 | 30,051 | 24,983 | 20,781 |
| **Men** | | | | | | |
| Non-persistence | 40.0% | 51.8% | 58.9% | 64.0% | 68.1% | 70.6% |
| Poor adherence | 10.0% | 5.1% | 3.4% | 2.6% | 2.3% | 2.1% |
| High adherence | 50.0% | 43.2% | 37.7% | 33.5% | 29.6% | 27.3% |
| N persistent cases | 7,569 | 5,557 | 4,246 | 3,323 | 2,567 | 1,991 |

**Refill gap period of 9 weeks; MPR ≥0.8 to define high compliance, <0.8 to define poor adherence.*

Results are sensitive to the refill gap length and to the MPR threshold. So, for example, 56.8%, 64.3% and 69.0% of women were considered as persistent after one year using a 5, 9 and 13 weeks refill gap respectively. The probability of being highly adherent was estimated on average at 94.1%, 89.1% and 75.7% assuming a threshold of 0.7, 0.8 or 0.9 for high adherence, respectively.

Re-initiation rates at one year were 25.4% for women and 21.5% for men, with a gap length of 9 weeks. These values were 42.1% and 34.9%, and 16.9% and 14.5% with refill gap periods of 5 and 13 weeks respectively. Mean MPR in the group of adherent and non-adherent patients ranged from 0.95 to 0.96 and from 0.47 to 0.70, respectively.

*MODEL VALIDATION*

The model performed well during validation, producing fracture incidence and mortality rates that were similar to the observed data. Under the assumption of no treatment, absolute lifetime risks of hip fracture and of any major osteoporotic fractures (hip, vertebral or wrist) were estimated, respectively, at 21.3% and 39.6% for a women aged 60 years with the fracture risk of the average population, in the range of estimates reported in the literature [46]. Expected life expectancies were also very similar to empirical data (differences of less than 0.1 years). Furthermore, tests on model parameters and modeling assumptions (such as the effects of changing the value of some parameters) were consistent with expected conclusions. Model-based projections of prescription drug use were also validated. Using the model, we calculated the percentage of patients on osteoporosis drug therapy at 3 years (including patients who have restarted therapy after stopping). These values were 52.5% and 35.6% for women and men respectively, consistent with estimates of 53.4% and 34.3% respectively from the adherence database. To determine the number of simulations, a varying number of trials (from 10,000 to 500,000) were run ten times and, as in the case of the Belgian version of the model [28], the distance between the upper and lower limits of

the 95% confidence intervals of the ICER of osteoporosis medications compared with no treatment reached a plateau from 200,000 trials.

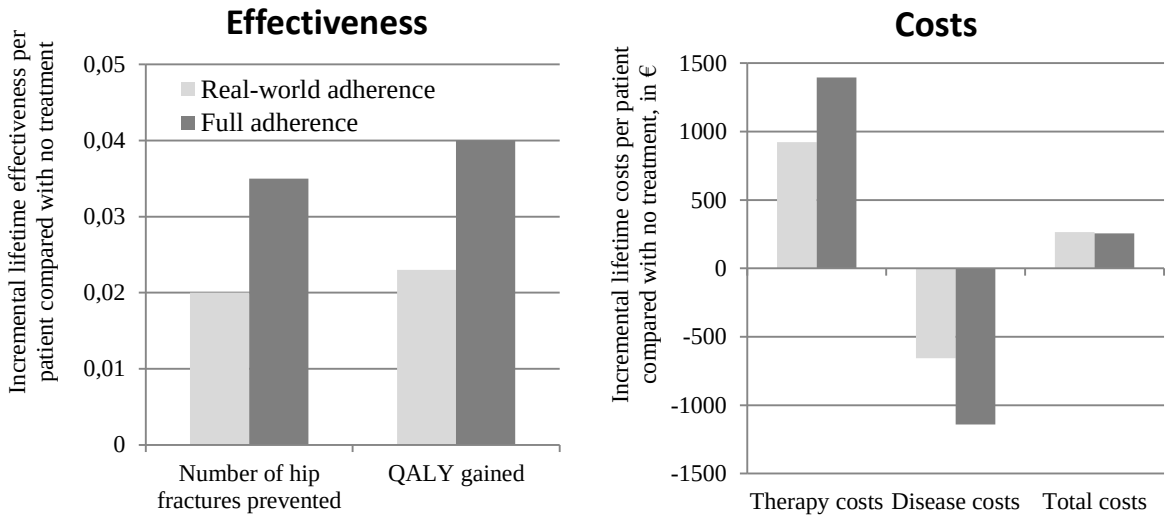
*SOCIETAL BURDEN: BASE-CASE ANALYSIS*

Mean lifetime number of hip fracture per patient was 0.49 for the no treatment scenario, 0.47 for the real-world scenario and 0.46 for the full adherence scenario. The equivalent values for any osteoporotic fractures were 1.32, 1.27 and 1.23, respectively (Table 3). Therefore, the lifetime number of hip and all osteoporotic fractures prevented in the case of real-world adherence represent 56.7% (95% CI 56.2%-57.3%) and 56.3% (95% CI 56.0%, 56.7%) to that estimated with full adherence scenario, respectively (Figure 2). The QALYs gain in the real-world adherence scenario was estimated at 56.0% (95% CI 54.6%, 57.5%) to that obtained under full adherence scenario. When assuming a 3-year time horizon, the number of fractures and the QALYs gain obtained at real-world adherence scenarios represent 65.7% (95% CI 65.9%-65.9%) and 65.4% (95% CI 64.0%, 66.9%) to that estimated with the full adherence scenario, respectively.

**Table 3|** *Clinical and economic burden of poor adherence with osteoporosis medications: base-case analysis (results at 3 years and over lifetime).*

| **Follow-up** | **Adherence scenario** | | | **Incremental values** | | |
|---|---|---|---|---|---|---|
| | **No Treat** | **RW** | **Full** | **RW vs No Treat** | **Full vs No Treat** | **Full vs RW** |
| **Patient cost over 3 years** | | | | | | |
| Treatment cost | 0 | 922 | 1,395 | 922 | 1,395 | 473 |
| Disease cost | 1,025 | 865 | 780 | -160 | -245 | -85 |
| Total cost | 1,025 | 1,787 | 2,175 | 762 | 1,150 | 388 |
| **Outcomes over 3 years** | | | | | | |
| Hip fractures per patient | 0.044 | 0.037 | 0.033 | -0.007 | -0.011 | -0.004 |
| All fractures per patient | 0.146 | 0.123 | 0.111 | -0.023 | -0.035 | 0.012 |
| QALYs per patient | 2.001 | 2.006 | 2.008 | 0.005 | 0.007 | 0.002 |
| **Patient cost over lifetime** | | | | | | |
| Treatment cost | 0 | 922 | 1,395 | 922 | 1,395 | 473 |
| Total disease cost | 11,425 | 10,769 | 10,284 | -656 | -1,140 | -485 |
| Acute fracture cost | 5,170 | 4,848 | 4,658 | -322 | -512 | -190 |
| Long-term fracture cost | 6,255 | 5,921 | 5,626 | -334 | -629 | -295 |
| Total healthcare cost | 11,425 | 11,691 | 11,679 | 266 | 255 | -12 |
| **Outcomes over lifetime** | | | | | | |
| Hip fractures per patient | 0.495 | 0.475 | 0.460 | -0.020 | -0.035 | -0.015 |
| All fractures per patient | 1.320 | 1.269 | 1.229 | -0.052 | -0.092 | -0.040 |
| QALYs per patient | 6.638 | 6.661 | 6.678 | 0.023 | 0.040 | 0.017 |
| **ICER (lifetime cost per lifetime QALY gained)** | | | | **11,834** | **6,341** | **-659** |
| (95% CI) | | | | (11,197-12,470) | (5,944-6,739) | (-1,488 -171) |

**Figure 2|** *Impact of medication adherence and persistence on outcomes (expressed as number of fractures prevented and quality-adjusted life-year) and on (treatment, disease and total) costs*




Compared with no treatment, real-world adherence scenario was associated with an additional lifetime cost of €266.3 and a 0.023 lifetime QALY gain of, giving an ICER of €11,834 per QALY gained (95% CI €11,197-€12,470) as illustrated on Table 3. The full adherence scenario was associated over lifetime with a lower cost and a higher QALY than the real-world adherence scenario, giving a negative ICER of €-659 per QALY (95% CI €-1,488, €-171). Full adherence is said to be cost-saving compared with real-world adherence.

For the 83,282 patients included in the database, the lifetime number of hip and of all osteoporotic types of fractures due to medication non-adherence was estimated at 1,271 (95% CI 1,238-1,304) and 3,340 (95% CI 3,295-3,386), respectively. These fractures result in a QALY loss of 1,470 (95% CI 1,398-1,544).

*SOCIETAL BURDEN: SENSITIVITY ANALYSES*

As observed on Table 4, the percentage of QALY loss due to poor adherence is substantially greater in men than in women. Other analysis suggests that the burden of adherence was primarily driven by persistence. Full adherence was responsible for 4.5% (= (3,340-3,191)/3,340) of the number of fractures, and 7.8% (=((100-56.3)-(100-59.7))/(100-56.3))) of the QALY loss, attributable to poor adherence. Definitions of non-adherence (i.e. refill gap period and MPR threshold) also had an impact on the results while baseline fracture risk and treatment efficacy markedly affected the number of fractures attributable to poor adherence. As more patients were good adherers when assuming a MPR threshold of 0.7, this scenario resulted in higher QALY gain and fractures prevented.

**Table 4**| *Sensitivity analyses on the clinical burden (expressed in % of QALY gain* and in number of osteoporotic fractures**) of poor adherence with osteoporosis medications*

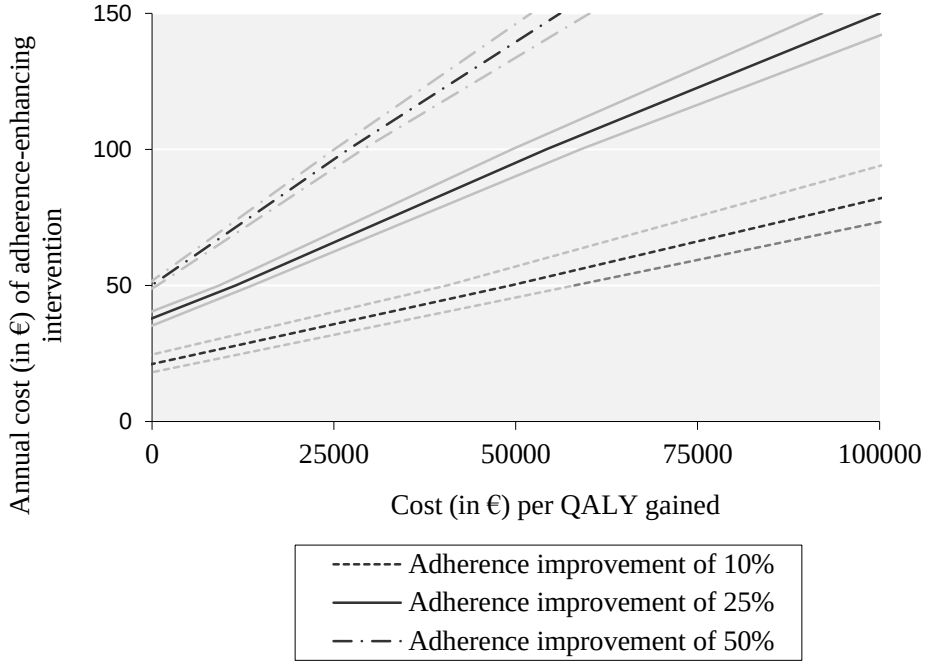
| | % of QALY gain | Number of fractures |
|---|---|---|
| Base-case analysis | 56.3 (54.5-57.5) | 3,340 (3,295-3,386) |
| Women | 57.6 (56.2-59.1) | 2,814 (2,771-2,856) |
| Men | 44.7 (42.6-46.8) | 527 (519-535) |
| 5-week refill gap | 50.9 (49.1-52.7) | 3,779 (3,741-3,818) |
| 13-week refill gap | 59.9 (58.2-61.6) | 3,062 (3,033-3,092) |
| Full compliance | 59.7 (58.2-61.2) | 3,191 (3,152-3,229) |
| MPR of 90% | 54.7 (53.3-56.1) | 3,612 (3,579-3,645) |
| MPR of 70% | 58.0 (56.9-59.2) | 3,266 (3,239-3,294) |
| Treatment efficacy +20% | 58.0 (56.9-59.1) | 3,985 (3,952-4,017) |
| Fracture risk +25% | 54.5 (52.7-56.3) | 4,342 (4,295-4,388) |
| Fracture risk -25% | 57.4 (56.1-58.5) | 2,405 (2,375-2,435) |

** Percentage of QALY gain for the simulated scenario compared to that obtained with the full adherence scenario.*

*POTENTIAL ADHERENCE-ENHANCING INTERVENTIONS*

Figure 3 presents the cost-effectiveness of potential adherence-enhancing interventions according to their cost and effect on adherence. So, for example, an intervention to improve adherence and persistence by 25% would result in an ICER of €11,511/QALY (95% CI €9,238-€13,784) and €54,182/QALY if the intervention cost an additional €50 and €100 per year, respectively. For potential interventions associated with a 50% increase in adherence rates, their cost-effectiveness was estimated at €26,999 per QALY (95% CI €25,034-€28,965) and €56,195 per QALY (95% CI €52,084-€60,166) for additional annual costs of €100 and €150, respectively. In other terms, a program to improve adherence and persistence by 10%, 25% or 50% would remain cost-effective at a threshold of €45,000 per QALY if it cost a maximum of €119.4, €299.0 and €726.3 annually per patient, respectively.

**Figure 3|** *Cost-effectiveness (expressed in cost (in €) per QALY gained) of adherence-enhancing interventions according to their cost and effect on adherence. The cost-effectiveness is graphically presented by the black lines and the grey lines represent the lower and upper limits of the 95% confidence interval.*




*QALY quality-adjusted life-year*

## DISCUSSION

Poor adherence undermines the potential effectiveness of osteoporosis medications in preventing fractures. Using simulation modeling, we estimated that approximately 50% of the expected benefits of osteoporosis medications were lost due to non-adherence. Moreover, poor adherence resulted in approximately a doubling of the cost per QALY gained from these medications. Sensitivity analyses in line with the results of other published studies [47] have shown that non-persistence is the leading problem with adherence: with more than 90% of the clinical burden of poor adherence resulting from non-persistence. We also investigated the economic value of improving patient adherence using a variety of hypothetical interventions and our results suggest favorable ICER for the majority of intervention effects and cost assumptions.

Studies in other countries have also shown that adherence with osteoporosis medications may have clinical and/or economic implications [16-19] but they have rarely examined the impact of both persistence and adherence on clinical and economic outcomes. A similar analysis was conducted in Belgian women using a prior version of the same model [17]. This analysis suggested that poor adherence with osteoporosis medications reduced the expected number of fractures and QALY gain by around 60%. The lower estimate in our study may be explained partially by longer refill gap

length for persistence and re-initiation of patients who discontinue therapy. Recent analyses have also suggested in other settings that interventions to improve osteoporosis medication adherence will likely have favorable ICERs if their efficacy can be sustained [17, 48].

Strengths of this study include the large-scale prescribing database that estimates persistence, adherence and re-initiation rates in both men and women with varying definitions for non-adherence (MPR threshold and gap lengths). We have also chosen a validated Markov microsimulation [23] that has been frequently used to assess the cost-effectiveness of osteoporosis management [18, 24-28]. Conservative assumptions were used and many sensitivity analyses were performed to show the potential impact of parameter assumptions and data on the results. National healthcare registers were also used to collect data for the model such as fracture incidence, fracture cost and the cost of medications.

Our study also presents some important improvements in the methodology to incorporate medication adherence and persistence in modeling of osteoporosis that increase the accuracy and reliability of the analysis. So, for the first time ever, patients can restart therapy in the model after discontinuation; the cost of highly and poorly adherent patients was related to the mean MPR of the group and a specific cost was assumed for patients who discontinued therapy prematurely. Moreover, patients were at risk of discontinuation in half of every cycle and the offset time was related to time on therapy [49]. One potential weakness of our analysis is that the impact of poor adherence on fracture efficacy was not available in Ireland and was derived from a large US study [10]. The impact of adherence on fracture risk was however of the same magnitude in many studies [13]. In addition, for patients who restart therapy after a period of interruption, the same adherence level was applied. Such patients may however resume at a less adherent level but this would require further investigation.

Another potential limitation of this study is that using prescription refill rates may overestimate medication adherence because it assumes that patients take all of the dispensed medications, but not necessarily persistence.. Prescription refill rates are, however, generally the only way to estimate adherence and represent a reliable and inexpensive way of evaluating persistence and adherence[50]. Another reason for the underestimation of the burden of poor adherence is the lack of inclusion of primary non-adherent patients. This term refers to patients who never fill a prescription. These patients were not included in the database since our study was based on pharmacy records of filled prescriptions. In addition, our manuscript deals primarily with direct costs. Decrease in medication adherence reduces significantly medications effects and subsequently, increases the need for surgery. Lack of adherence and the subsequent fracture increase also impact on all health care resources utilization including physiotherapy and occupational therapy. Caregiver costs as well as loss of productivity and absenteeism were also shown to be significant in

osteoporosis management [51] and lack of adherence in osteoporosis medications may potentially result in over utilization of pain medication which can also be linked to decrease productivity,

Another limitation is that highly adherent patients will achieve reductions in fracture risk based on meta-analysis from published clinical trials. This seems plausible because trials are likely to reflect the highest achievable rate of adherence in actual practice. However, because adherence in all the trials (and not unique to osteoporosis) is not optimal for all the patients, the efficacy from these trials is likely to be reduced to some degree because of non-adherence and non-persistence. Therefore, we probably underestimated the true underlying risk reduction with therapy [52]. Another limitation is the use of a dichotomous measure for persistence and adherence which is likely to result in a loss of power between patients who are fully non-adherent and those who are just below the cut-off point for adherence.

Finally, like all models, several limitations must be taken into account. The most important are availability of data. Although much of the data used to construct the model was extracted from the Irish datasets, some data were extrapolated from other countries, as was the case for the Belgian model [23]. In particular, the impacts of fractures on health-related quality of life were generally derived from a Swedish study [53]. Although fracture disutility tends to be similar between several countries [37], differences may be present between Irish and Swedish patients. It could be argued that hip fractures are the fracture type considered to be the key driver in the cost-effectiveness of osteoporosis medications [54] and their incidence and costs were estimated from a local database. Potential limitations of the model have been previously extensively discussed [17, 23]. In particular, threshold for adherence remains uncertain since there is no clinically meaningful definition for high adherence. Further studies should re-examine the 0.8 threshold for adherence.

Generalizability of the results to the whole population may also be uncertain since adherence and persistence data were based on a sub-population in Ireland which is more socially deprived and elderly. However, we do not expect that adherence and persistence data will substantially differ.

Our analysis may have important clinical and economic implications. First, it suggests that poor adherence can be considered as the critical hurdle to osteoporosis management. Improving adherence is therefore becoming urgent but remains a complex issue. Behavioral programs to improve adherence with osteoporosis medications have been initiated but few interventions were efficacious, and no clear trends regarding successful intervention techniques can be identified [21]. New formulations and longer dosages regimens have also been recently available, which in principle can help to improve adherence [55]. Less frequent dosing regimens have been frequently associated with better adherence [56, 57]. There is a need to conduct additional research with behavioral interventions and to consider the impact of specific pharmacological treatments on medication adherence. As many determinants of poor adherence have been identified [58, 59], understanding patient's preferences for osteoporosis treatments and involving patients into clinical

decision-making may certainly be useful in optimizing treatment selection and in improving adherence to therapy. Second, our analysis highlights the importance of integrating medication adherence and persistence in pharmacoeconomic analyses conducted in osteoporosis [26-29]. Poor adherence represents a new perspective on health economic assessment in osteoporosis [60] and our study may provide an interesting background for integrating medication adherence and persistence.

In summary, this analysis suggests that poor adherence with osteoporosis medications results in approximately a 50% reduction in the potential benefits observed in clinical trials and a doubling of the cost per QALY gained from these medications. Moreover, depending on their costs and outcomes, programs to improve adherence have the potential to be an efficient use of resources.

## REFERENCES


1. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int. 2000;11(8):669-74.
2. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15(1):38-42.
3. Lips P, van Schoor NM. Quality of life in patients with osteoporosis. Osteoporos Int. 2005;16(5):447-55.
4. Report of the National Steering Group on the Prevention of Falls in Older People and the Prevention and Management of Osteoporosis throughout Life. Strategy to Prevent Falls and Fractures in Ireland's Ageing Population. 2008. Available from http://www.hse.ie/eng/services/Publications/services/Older/Strategy_to_Prevent_Falls_and_Fractures_in_Ireland%E2%80%99s_Ageing_Population_-_Full_report.pdf [Accessed May 1, 2011].
5. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2008;19(4):399-428.
6. Fleurence RL, Iglesias CP, Torgerson DJ. Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. Osteoporos Int. 2006;17(1):29-40.
7. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis-a review of the literature and a reference model. Osteoporos Int. 2007;18(1):9-23.
8. Elliot-Gibson V, Bogoch ER, Jamal SA, Beaton DE. Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: a systematic review. Osteoporos Int. 2004;15(10):767-78.
9. Rabenda V, Vanoverloop J, Fabri V, Mertens R, Sumkay F, Vannecke C, et al. Low incidence of anti-osteoporosis treatment after hip fracture. J Bone Joint Surg Am. 2008;90(10):2142-8.
10. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006;38(6):922-8.
11. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int. 2010;21(11):1943-51.
12. Rabenda V, Hiligsmann M, Reginster J-Y. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. Expert Opin Pharmacother. 2009;10(14):2303-15.
13. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RMC, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med. 2009;122(2 Suppl):S3-13.
14. Hughes D, Cowell W, Koncz T, Cramer J. Methods for integrating medication compliance and persistence in pharmacoeconomic evaluations. Value Health. 2007;10(6):498-509.
15. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. Health Econ. 2001;10(7):601-15.
16. Danese MD, Badamgarav E, Bauer DC. Effect of adherence on lifetime fractures in osteoporotic women treated with daily and weekly bisphosphonates. J Bone Miner Res. 2009;24(11):1819-26.

17. Hiligsmann M, Rabenda V, Bruyere O, Reginster J-Y. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy. 2010;96(2):170-7.
18. Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY. Potential Clinical and Economic Impact of Nonadherence with Osteoporosis Medications. Calcif Tissue Int. 2010;86:202-10.
19. Landfeldt E, Lundkvist J, Strom O. The societal burden of poor persistence to treatment of osteoporosis in Sweden. Bone. 2011;48(2):380-8.
20. Avis NE, Smith KW, McKinlay JB. Accuracy of perceptions of heart attack risk: what influences perceptions and can they be changed? Am J Public Health. 1989;79(12):1608-12.
21. Gleeson T, Iversen MD, Avorn J, Brookhart AM, Katz JN, Losina E, et al. Interventions to improve adherence and persistence with osteoporosis medications: a systematic literature review. Osteoporos Int. 2009;20(12):2127-34.
22. Hiligsmann M, Salas M, Hughes DA, Manias E, Gwadry-Sridhar F, Linck P, et al. Most Effective Patient Compliance Interventions with Osteoporosis Medications. Value in Health. 2011;14:A130.
23. Hiligsmann M, Ethgen O, Bruyere O, Richy F, Gathon HJ, Reginster JY. Development and Validation of a Markov Microsimulation Model for the Economic Evaluation of Treatments in Osteoporosis. Value Health. 2009;12(5):687-96.
24. Hiligsmann M, Bruyere O, Reginster JY. Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women. Osteoporos Int. 2010;21(1):157-65.
25. Hiligsmann M, Bruyere O, Reginster JY. Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women. Osteoporos Int. 2010;21(1):157-65.
26. Hiligsmann M, Gathon HJ, Bruyere O, Ethgen O, Rabenda V, Reginster JY. Cost-Effectiveness of Osteoporosis Screening Followed by Treatment: The Impact of Medication Adherence. Value Health. 2010;13(4):394-401.
27. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. Bone. 2010;47(1):34-40.
28. Hiligsmann M, Reginster JY. Cost Effectiveness of Denosumab Compared with Oral Bisphosphonates in the Treatment of Post-Menopausal Osteoporotic Women in Belgium. Pharmacoeconomics. 2011;29(10):895-911
29. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. Bone. 2000;27(5):585-90.
30. Johansson H, Kanis JA, McCloskey EV, Oden A, Devogelaer JP, Kaufman JM, et al. A FRAX(R) model for the assessment of fracture probability in Belgium. Osteoporos Int. 2011;22(2):453-61.
31. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12(5):417-27.
32. Haentjens P, Magaziner J, Colon-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med. 2010;152(6):380-90.
33. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. Osteoporos Int. 2004;15(2):108-12.
34. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. Bone. 2003;32(5):468-73.
35. Beringer TR, Clarke J, Elliott JR, Marsh DR, Heyburn G, Steele IC. Outcome following proximal femoral fracture in Northern Ireland. Ulster Med J. 2006;75(3):200-6.

36. Melton LJ, 3rd, Gabriel SE, Crowson CS, Tosteson AN, Johnell O, Kanis JA. Cost-equivalence of different osteoporotic fractures. Osteoporos Int. 2003;14(5):383-8.
37. Hiligsmann M, Ethgen O, Richy F, Reginster JY. Utility values associated with osteoporotic fracture: a systematic review of the literature. Calcif Tissue Int. 2008;82(4):288-92.
38. National Institute for Health and Clinical Excellence. Systematic reviews of clinical effectiveness prepared for the guideline "Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk." Available from: http://www.nice.org.uk/nicemedia/live/11621/42362/42362.pdf. [Accessed March 1, 2011].
39. Stock JL, Bell NH, Chesnut CH, 3rd, Ensrud KE, Genant HK, Harris ST, et al. Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. Am J Med. 1997;103(4):291-7.
40. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11(1):44-7.
41. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med. 2009;122(2 Suppl):S3-13.
42. Strom O, Borgstrom F, Kanis JA, Jonsson B. Incorporating adherence into health economic modelling of osteoporosis. Osteoporos Int. 2010;20(1):23-34.
43. Gallagher AM, Rietbrock S, Olson M, van Staa TP. Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res. 2008;23(10):1569-75.
44. Landfeldt E, Strom O, Robbins S, Borgstrom F. Adherence to treatment of primary osteoporosis and its association to fractures-the Swedish Adherence Register Analysis (SARA). Osteoporos Int. 2012;23(2):433–43
45. Health Information and Quality Authority. Guidelines for the economic evaluation of health technologies in Ireland. Available from: http://www.hiqa.ie/healthcare/health-technology-assessment/guidelines. [Accessed March 1, 2011].
46. Hiligsmann M, Bruyere O, Ethgen O, Gathon HJ, Reginster JY. Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women. Bone. 2008;43(6):991-4.
47. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336(7653):1114-7.
48. Patrick AR, Schousboe JT, Losina E, Solomon DH. The economics of improving medication adherence in osteoporosis: validation and application of a simulation model. J Clin Endocrinol Metab. 2011;96(9):2762-70
49. Strom O, Borgstrom F, Kanis JA, Jonsson B. Incorporating adherence into health economic modelling of osteoporosis. Osteoporos Int. 2009;20(1):23-34.
50. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther. 2001;26(5):331-42.
51. Rabenda V, Manette C, Lemmens R, Mariani AM, Struvay N, Reginster JY. The direct and indirect costs of the chronic management of osteoporosis: a prospective follow-up of 3440 active subjects. Osteoporos Int. 2006;17(9):1346-52.
52. Danese MD, Badamgarav E, Bauer DC. Effect of adherence on lifetime fractures in osteoporotic women treated with daily and weekly bisphosphonates. J Bone Miner Res. 2009;24(11):1819-26.

53. Borgstrom F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos Int. 2006;17(5):637-50.
54. Borgstrom F, Johnell O, Kanis JA, Oden A, Sykes D, Jonsson B. Cost effectiveness of raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation based on the MORE study. Pharmacoeconomics. 2004;22(17):1153-65.
55. Lekkerkerker F, Kanis JA, Alsayed N, Bouvenot G, Burlet N, Cahall D, et al. Adherence to treatment of osteoporosis: a need for study. Osteoporos Int. 2007;18(10):1311-7.
56. Kendler DL, Bessette L, Hill CD, Gold DT, Horne R, Varon SF, et al. Preference and satisfaction with a 6-month subcutaneous injection versus a weekly tablet for treatment of low bone mass. Osteoporos Int. 2010;21(5):837-46.
57. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clinical therapeutics. 2001;23(8):1296-310.
58. Jones TJ, Petrella RJ, Crilly R. Determinants of persistence with weekly bisphosphonates in patients with osteoporosis. J Rheumatol. 2008;35(9):1865-73.
59. Rossini M, Bianchi G, Di Munno O, Giannini S, Minisola S, Sinigaglia L, et al. Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int. 2006;17(6):914-21.
60. Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. Osteoporos Int. 2011; 22(10):2565-73.

# APPENDIX 1. ADDITIONAL MODEL ASSUMPTIONS.

This appendix aims to provide additional details on the data and assumptions used in the model. It includes information on: 1) increased risk attributable to osteoporosis, 2) fracture risk adjustment during simulation after fractures, 3) excess mortality after fractures, 4) long-term costs of hip fractures and (5 health state utility values.

**1) Increased risk attributable to osteoporosis**

In order to accurately reflect the risk in the population receiving osteoporosis medications (assumed to be the population with a bone mineral density (BMD) T-score ≤-2.5) in comparison with that of the general population, the risk of fracture in the general population was adjusted by relative risk parameters.

Kanis et al. have suggested a method to adjust the fracture risk according to BMD [1]. This method allows estimating the relative risk of individuals below a threshold value compared with the fracture risk of the total population of that age (e.g. all those with osteoporosis).

The risk of fracture of those with BMD below the threshold for BMD ( $g$ ) at a certain age is

$$\textit{Yearly incidence of the age group } X \ \Phi\left(\left(g-\mu\right)/\sigma + \ln(RR)\right)/\Phi\left(\left(g-\mu\right)/\sigma\right)$$

*"Where $\mu$ is the mean and $\sigma$ is the standard deviation of BMD at the current age and ln (RR) is the e-log of the risk ratio of an individual with one standard deviation lower BMD as compared with another. $\Phi$ is the normal distribution function with equal 0 and standard deviation equal 1.[1]*

The mean and number of standard deviations of BMD were derived from the NHANES III [2] database for white men and women aged 60-69 years, 70-79 years and over 80 years. One standard deviation decrease in BMD was associated with an increase in age-adjusted relative risk of 1.8, 1.4 and 1.6 for clinical vertebral, wrist and other osteoporotic fracture, respectively [3]. The age-adjusted relative risk for hip fracture ranged from 3.1 at 60 years to 1.9 at 85 years [4].

**2) Fracture risk adjustment during simulation**

Fracture risk was adjusted when a new fracture occurred during the simulation. An increased risk of subsequent fractures was modeled for women who had a prior fracture at the same location. These increased relative risks were 4.4, 2.3, 3.3, and 1.9 for vertebral, hip, wrist, and other fractures, respectively [5]. As a multiplicative hypothesis could not be supported at this time, we conservatively did not model an increased risk of subsequent fractures at sites different from that of the prior fractures. However, an increased relative risk of 2.3 is modeled for a hip fracture after a vertebral fracture, because this effect is largely supported by the literature [5]. All these increased relative risks were increased by a factor of 1.7 during the year following the fracture [6] and were reduced by 10% per decade above the age of 70 years [7]. Further subsequent fractures of the same type are assumed to have no additional effect.

**3) Excess mortality after fractures**

Based on the results of a recent meta-analysis [8], we assumed that hip fracture increases the probabilities of death in women (men) by 4.53 (5.75) in the first six months following the fracture (= mean of the periods 0-3 and 3-6 months), by 1.755 (2.315) in the period 6-12 months and by 1.779 (1.691) in subsequent years. This last was estimated as the mean of the excess mortality estimated between 1 and 10 years.

The increased mortality following a clinical vertebral fracture has been found in many studies to be very similar and even slightly higher than those of a hip fracture [9-12]. Therefore, we suggested an impact of clinical vertebral fracture similar to that of hip fracture.

It is also assumed that other osteoporotic fractures, included wrist fractures, are not associated with an increased mortality that could be attributable to the fracture, and this is consistent with published studies [12, 13].

We also suggested in a conservative manner that a second and further fractures at the same site will cause no greater excess mortality, except the increase for the year after they occur. However, we do assume an interaction of excess mortality between a vertebral and an hip fracture, based on the result of Cauley et al.(2000) [12].

**4) Long-term cost of hip fractures**

The long-term costs of hip fractures have been based on the proportion of patients being institutionalized following the fracture, estimated at 10% [14]. In economic models, it is assumed that a patient who enter into a nursing home will remain there for the rest of their lives [15] and thus the annual cost of being in the nursing home is added into the model for each remaining year of the patient's life. However, this is a simplification providing a cost overestimation because the individuals might have been institutionalized later in life in any case, regardless of their hip fracture. Therefore, it is important to estimate only the long-term costs attributable to hip fracture, which could be reduced through fracture prevention [16]. In order to estimate the total cost attributable to fracture, we first reduced the proportion of individuals in a nursing home following a fracture (=100%) each year by the institutionalization rate in the general population. The annual hip fracture cost was obtained by multiplying the proportion of fractures related to institutionalization with the discounted annual cost of institutionalization (€49,539 per year, cost of shared private room). Then, we summed these values for each year until the age of average life expectancy. The proportion of long-term costs attributable to hip fracture was therefore estimated respectively at 97.0% (97.8%), 95.3% (96.1%) and 89.8% (91.3%) for women (men) aged 60-69, 70-79 and over 80 years, respectively. So, a 60 year old woman institutionalized after a hip fracture would have an annual long-term cost, for their remaining life years, equal to 0.970 X €49,539 = €48,449. If the fracture occurs at the age of 70 years, the annual long-term cost will be 0.953 X €49,539 = €47,211. The annual mean long-term cost of hip fracture will therefore depend on the age of the patient at the fracture event and it was, of course, discounted and therefore not constant over time.

**5) Health state utility values**

The relative reductions due to fractures in the year following the fracture and in subsequent years were applied to both women and men. The systematic review from which data were retrieved [17] included studies that were composed mainly of postmenopausal women. Few studies have specifically estimated the impact of fractures on quality of life in populations of men. However, the decrease in quality of life due to osteoporotic fractures in men appears comparable to that caused by post-menopausal osteoporotic women [18, 19]. Some reference values for fracture disutility (i.e. the 1-year impact of clinical vertebral and wrist fractures) were derived from a Swedish study, in which the mean reduction in quality of life was estimated based on the collection of utility data with the EQ-5D questionnaire at baseline, 4 months and 12 months after different fractures on a patient sample of 635 male and female patients [20].

**6) References**

1. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. Bone. 2000;27(5):585-90.
2. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int. 1998;8(5):468-89.
3. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312(7041):1254-9.
4. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res. 2005;20(7):1185-94.
5. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15(4):721-39.
6. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Fracture risk following an osteoporotic fracture. Osteoporos Int. 2004;15(3):175-9.
7. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004;35(2):375-82.
8. Haentjens P, Magaziner J, Colon-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Inter Med. 2010;152(6):380-90.
9. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15(1):38-42.
10. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. Osteoporos Int. 2004;15(2):108-12.

11. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. Bone. 2003;32(5):468-73.
12. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11(7):556-61.
13. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ, 3rd. Population-based study of survival after osteoporotic fractures. Am J Epidemiol. 1993;137(9):1001-5.
14. Beringer TR, Clarke J, Elliott JR, Marsh DR, Heyburn G, Steele IC. Outcome following proximal femoral fracture in Northern Ireland. Ulster Med J. 2006;75(3):200-6.
15. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis--a review of the literature and a reference model. Osteoporos Int. 2007;18(1):9-23.
16. Borgstrom F, Strom O. Long term hip fracture related to institutionalization. Osteoporos Int. 2007;18 (Suppl 1):S29-S175.
17. Hiligsmann M, Ethgen O, Richy F, Reginster JY. Utility values associated with osteoporotic fracture: a systematic review of the literature. Calcif Tissue Int. 2008;82(4):288-92.
18. Adachi JD, Ioannidis G, Pickard L, Berger C, Prior JC, Joseph L, et al. The association between osteoporotic fractures and health-related quality of life as measured by the Health Utilities Index in the Canadian Multicentre Osteoporosis Study (CaMos). Osteoporos Int. 2003;14(11):895-904.
19. Papaioannou A, Kennedy CC, Ioannidis G, Sawka A, Hopman WM, Pickard L, et al. The impact of incident fractures on health-related quality of life: 5 years of data from the Canadian Multicentre Osteoporosis Study. Osteoporos Int. 2009;20(5):703-14.
20. Borgstrom F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos Int. 2006;17(5):637-50.

# APPENDIX 2. ADDITIONAL RESULTS AND SENSITIVITY ANALYSES

This appendix aims to provide the readers with additional results.

Table 1 present persistence and adherence data with osteoporosis medications in Irish men and women according to different refill gap periods (from 5 to 13 weeks).

**Table 1|** *Persistence and adherence data according to different refill gap periods**

| Follow-up | 6 month | 1 year | 1.5 years | 2 years | 2.5 years | 3 years |
|---|---|---|---|---|---|---|
| **Women** | | | | | | |
| *9 weeks refill gap period (base-case)* | | | | | | |
| Non-persistence | 26.2% | 35.7% | 41.9% | 47.3% | 51.9% | 55.0% |
| Poor adherence | 13.1% | 7.7% | 5.9% | 4.7% | 4.1% | 3.5% |
| High adherence | 60.8% | 56.6% | 52.2% | 48.0% | 43.9% | 41.5% |
| *5 weeks refill gap period* | | | | | | |
| Non-persistence | 31.4% | 43.2% | 51.1% | 59.2% | 64.6% | 67.8% |
| Poor adherence | 9.5% | 4.9% | 2.2% | 1.7% | 1.5% | 1.4% |
| High adherence | 59.0% | 51.9% | 46.6% | 39.1% | 33.9% | 30.8% |
| *13 weeks refill gap period* | | | | | | |
| Non-persistence | 22.5% | 31.0% | 36.7% | 41.5% | 45.8% | 48.8% |
| Poor adherence | 15.8% | 10.5% | 8.4% | 6.9% | 6.2% | 5.4% |
| High adherence | 61.7% | 58.6% | 54.9% | 51.6% | 48.0% | 45.8% |
| **Men** | | | | | | |
| *9 weeks refill gap period (base-case)* | | | | | | |
| Non-persistence | 40.0% | 51.8% | 58.9% | 64.0% | 68.1% | 70.6% |
| Poor adherence | 10.0% | 5.1% | 3.4% | 2.6% | 2.3% | 2.1% |
| High adherence | 50.0% | 43.2% | 37.7% | 33.5% | 29.6% | 27.3% |
| *5 weeks refill gap period* | | | | | | |
| Non-persistence | 45.4% | 58.2% | 66.1% | 72.3% | 76.5% | 78.9% |
| Poor adherence | 8.3% | 3.9% | 1.7% | 1.3% | 1.2% | 1.2% |
| High adherence | 60.3% | 52.9% | 47.2% | 39.5% | 34.2% | 31.0% |
| *13 weeks refill gap period* | | | | | | |
| Non-persistence | 36.7% | 47.7% | 54.9% | 59.9% | 64.1% | 66.7% |
| Poor adherence | 15.4% | 10.2% | 7.5% | 6.0% | 5.3% | 4.9% |
| High adherence | 62.1% | 58.8% | 56.3% | 52.5% | 48.9% | 46.3% |

** MPR of 0.8 or more to define high adherence*

Table 2 shows the repartition of persistent patients according to MPR (Medical Possession Ratio) threshold to define high adherence.

**Table 2|** *Repartition of persistent patients according to MPR threshold*

| Follow-up | 6 month | 1 year | 1.5 years | 2 years | 2.5 years | 3 years |
|---|---|---|---|---|---|---|
| **Women** | | | | | | |
| *MPR of 0.8 (base-case)* | | | | | | |
| Poor adherence | 17.7% | 11.9% | 10.1% | 8.9% | 8.4% | 7.8% |
| High adherence | 82.3% | 88.1% | 89.9% | 91.1% | 91.2% | 92.2% |
| *MPR of 0.7* | | | | | | |
| Poor adherence | 8.9% | 6.5% | 5.6% | 5.0% | 4.7% | 4.4% |
| High adherence | 91.1% | 93.5% | 94.4% | 95.0% | 95.3% | 95.6% |
| *MPR of 0.9* | | | | | | |
| Poor adherence | 23.8% | 26.7% | 24.9% | 24.5% | 23.6% | 22.5% |
| High adherence | 76.2% | 73.3% | 75.1% | 75.5% | 76.4% | 77.5% |
| **Men** | | | | | | |
| *MPR of 0.8 (base-case)* | | | | | | |
| Poor adherence | 16.7% | 10.5% | 8.3% | 7.3% | 7.3% | 7.0% |
| High adherence | 83.3% | 89.5% | 91.7% | 92.7% | 92.7% | 93.0% |
| *MPR 0.7* | | | | | | |
| Poor adherence | 8.1% | 5.0% | 4.2% | 4.1% | 3.8% | 3.4% |
| High adherence | 91.9% | 95.0% | 95.8% | 95.9% | 96.2% | 96.6% |
| *MPR 0.9* | | | | | | |
| Poor adherence | 24.2% | 25.9% | 23.8% | 23.2% | 22.6% | 21.5% |
| High adherence | 75.8% | 74.1% | 76.2% | 76.8% | 77.4% | 78.6% |

In table 3, the mean MPR in the groups of highly and poorly adherent patients was estimated. These values were used in the model to adjust drug cost in both groups.

**Table 3|** *Mean medical possession ratio (MPR) in the groups of highly* and poorly adherent patients*

| Follow-up | 6 month | 1 year | 1.5 years | 2 years | 2.5 years | 3 years |
|---|---|---|---|---|---|---|
| **Women** | | | | | | |
| *Refill gap period of 9 weeks (Base-case)* | | | | | | |
| Poor adherence | 0.679 | 0.656 | 0.636 | 0.615 | 0.597 | 0.581 |
| High adherence | 0.962 | 0.957 | 0.956 | 0.954 | 0.953 | 0.954 |
| *5-weeks refill gap* | | | | | | |
| Poor adherence | 0.701 | 0.633 | 0.587 | 0.529 | 0.496 | 0.472 |
| High adherence | 0.964 | 0.961 | 0.962 | 0.962 | 0.963 | 0.963 |
| *13-weeks refill gap* | | | | | | |
| Poor adherence | 0.658 | 0.650 | 0.650 | 0.635 | 0.627 | 0.618 |
| High adherence | 0.962 | 0.955 | 0.955 | 0.950 | 0.949 | 0.949 |
| **Men** | | | | | | |
| *Refill gap period of 9 weeks (Base-case)* | | | | | | |
| Poor adherence | 0.680 | 0.680 | 0.640 | 0.601 | 0.606 | 0.616 |
| High adherence | 0.962 | 0.957 | 0.956 | 0.953 | 0.953 | 0.953 |
| *5-weeks refill gap* | | | | | | |
| Poor adherence | 0.704 | 0.661 | 0.581 | 0.516 | 0.483 | 0.508 |
| High adherence | 0.964 | 0.962 | 0.963 | 0.962 | 0.962 | 0.962 |
| *13-weeks refill gap* | | | | | | |
| Poor adherence | 0.656 | 0.664 | 0.646 | 0.630 | 0.627 | 0.640 |
| High adherence | 0.962 | 0.956 | 0.953 | 0.950 | 0.948 | 0.949 |

** MPR of 0.8 or more to define high adherence*

Table 4 presents, for the 83,282 patients included in the database, the repartition of the number of hip and of all osteoporotic types of fractures due to medication poor adherence and persistence according to sex and age groups. The number of fractures resulting from poor was determined by multiplying the difference between the lifetime number of fractures in the full and real-world adherence scenarios by the number of patients included in the different age and sex groups.

**Table 4|** *Number (95% confidence interval) of hip and of all osteoporotic fractures due to poor adherence, according to sex and age groups. Y: years*

| | 55-64 y | 65-69 y | 70-74 y | + 75y | Total |
|---|---|---|---|---|---|
| **Hip fractures** | | | | | |
| Women | 41 (36-46) | 71 (67-74) | 231 (221-242) | 752 (722-781) | 1094 (1064-1125) |
| Men | 8 (7-9) | 10 (9-11) | 37 (36-38) | 121 (117-126) | 177 (172-181) |
| Total | 49 (44-53) | 81 (77-84) | 268 (258-279) | 873 (842-904) | 1271 (1238-1304) |
| **All osteoporotic fractures** | | | | | |
| Women | 149 (141-156) | 236 (230-242) | 655 (638-671) | 1774 (1735-1831) | 2814 (2771-2856) |
| Men | 32 (30-33) | 34 (33-35) | 95 (93-96) | 366 (359-374) | 527 (519-535) |
| Total | 180 (173-188) | 270 (263-277) | 749 (732-767) | 2140 (2100-2181) | 3340 (3295-3386) |

Table 5 presents the incremental cost-effectiveness ratio between the adherence scenarios according to age and sex groups. The ICERs improved with increasing age and was lower in women than in men, especially for those aged over 75 years as the benefits of prevented fractures is higher in women given the higher life expectancy.

**Table 5|** *Cost-effectiveness (expressed in cost (in €) per QALY gained) between adherence scenarios according to age and sex. 95% confidence intervals are provided in parentheses. RW: Real-World. Treat: Treatment. Y: year.*

| | RW vs No Treat | Full vs No Treat | Full vs RW |
|---|---|---|---|
| **Women** | | | |
| 55-64 y | 69,704 | 57,033 | 40,574 |
| | (54,088-85,119) | (44,903-69,164) | (24,353-56,795) |
| 65-69 y | 29,127 | 18,579 | 5,465 |
| | (24,455-33,800) | (16,565-20,593) | (3,153-7,777) |
| 70-74 y | 10,221 | 4,313 | -3,635 |
| | (8,757-11,686) | (3,314-5,311) | (-5,954;-1,317) |
| + 75 y | 1,823 | -2,111 | -7,587 |
| | (341-3,305) | (-2,901;-1,320) | (-9,083;-6,092) |
| Total | 10,253 | 4,878 | -2,437 |
| | (9,598;10,908) | (4,443-5,313) | (-3,348;-1,526) |
| **Men** | | | |
| 55-64 y | 78,409 | 56,438 | 38,899 |
| | (62,404-94,415) | (45,597-67,278) | (30,491-47,308) |
| 65-69 y | 46,183 | 35,013 | 25,514 |
| | (38,408-53,959) | (30,548-39,478) | (21,629-29,399) |
| 70-74 y | 27,921 | 15,750 | 6,514 |
| | (25,390-30,452) | (14,388-17,112) | (5,144-7,884) |
| + 75 y | 15,661 | 8,932 | 3,393 |
| | (13,487-17,835) | (8,075-9,790) | (2,419-4,367) |
| Total | 26,159 | 16,625 | 8,916 |
| | (24,260-28,058) | (15,840-17,410) | (8,300-9,532) |

Table 6 provides additional sensitivity analyses on the incremental cost-effectiveness ratio between the adherence scenarios.

**Table 6|** *Sensitivity analyses on the incremental cost-effectiveness ratio (expressed in cost (in €) per QALY gained) between adherence scenarios*

| | **RW *vs* No Treat** | **Full *vs* No Treat** | **Full *vs* RW** |
|---|---|---|---|
| **Base-case** | 11,834<br>(11,197-12,470) | 6,341<br>(5,944-6,739) | -659<br>(-1,488 -171) |
| Discount rates 3% | 9,498<br>(8,692-10,304) | 4,274<br>(3,686-4,863) | -2,646<br>(-3,496 -1,800) |
| Fracture risk +25% | 2,894<br>(2,216-3,572) | -2,186<br>(-2,637-1,735) | -8,274<br>(-9,408-7,141) |
| Fracture risk -25% | 25,767<br>(24,418-27,115) | 18,620<br>(17,986-19,253) | 8,993<br>(8,251-9,735) |
| Fracture cost +25% | 2,489<br>(1,361-3,617) | -2,852<br>(-3,579 -2,124) | -10,575<br>(-12,598 -8,553) |
| Fracture cost -25% | 19,358<br>(18,401-20,316) | 14,408<br>(13,914-14,903) | 7,455<br>(6,401-8,510) |
| Fracture disutility +25% | 10,494<br>(9,470-11,518) | 5,491<br>(5,122-5,859) | -797<br>(-1,613, 18) |
| Fracture disutility -25% | 13,390<br>(12,362-14,418) | 6,904<br>(6,555-7,254) | -1,507<br>(-2,508 -506) |
| No excess mortality | 11,103<br>(10,034-12,173) | 2,121<br>(1,238-3,004) | -10,164<br>(-12,012 -8,316) |
| Treatment efficacy +20% | 4,570<br>(4,024-5,116) | 342<br>(27-657) | -5,504<br>(-6,448 -4,561) |
| Refill gap 5 weeks | 14,568<br>(13,727-15,588) | 6,872<br>(6,363-7,381) | -1,196<br>(-2,104 -288) |
| Refill gaps 13 weeks | 10,786<br>(10,152-11,421) | 6,392<br>(5,777-7,007) | -173<br>(-1,099, 753) |
| Full compliance | 11,487<br>(10,624-12,351) | 6,386<br>(5,821-6,950) | -1,175<br>(-2,224 -127) |
| MPR of 0.9 | 13,975<br>(12,976-14,975) | 6,708<br>(6,140-7,275) | -2,063<br>(-3,346 -781) |
| MPR of 0.7 | 10,557<br>(10,059-11,055) | 6,169<br>(5,819-6,519) | 98<br>(-471 668) |

Table 7 presents additional sensitivity analyses on the cost-effectiveness of adherence-enhancing interventions compared with real-world adherence scenario, including interventions associated with one-time cost at baseline (such as the cost of an education program).

**Table 7**| *Sensitivity analyses on the cost-effectiveness (expressed in cost (in €) per QALY gained) of adherence-enhancing interventions*

| | **Adherence improvement** | | |
|---|---|---|---|
| | **10%** | **25%** | **50%** |
| **€100 per year of treatment** | | | |
| Base-case | 128,621 (108,259-148,984) | 54,182 (49,476-58,889) | 26,999 (25,034-28,965) |
| Men | 128,898 (105,842-151,955) | 60,914 (53,693-68,134) | 35,509 (33,485-38,333) |
| Women | 128,574 (102,080-155,069) | 52,951 (47,661-58,240) | 25,482 (23,214-27,750) |
| +75 years | 110,509 (69,116-151,902) | 41,859 (31,543-52,175) | 18,549 (16,877-20,222) |
| **One-time cost** | | | |
| €100 | 32,906 (26,395-39,416) | -5,686 (-7,704 -3,667) | -15,571 (-17,080 -14,062) |
| €200 | 95,245 (79,912-110,559) | 19,790 (17,176-22,404) | -4,394 (-5,428 -3,361) |
| €300 | 157,565 (133,027-182,103) | 45,266 (41,156-49,376) | 7,445 (6,599-8,291) |
| €400 | 216,894 (186,067-253,722) | 70,741 (64,888-76,594) | 18,953 (17,519-20,388) |

# CHAPTER 7

## INTERVENTIONS TO IMPROVE OSTEOPOROSIS MEDICATION ADHERENCE AND PERSISTENCE: A SYSTEMATIC REVIEW AND LITERATURE APPRAISAL BY THE ISPOR MEDICATION ADHERENCE & PERSISTENCE SPECIAL INTEREST GROUP

**Hiligsmann M**, Salas M, Hughes DA, Manias F, Gwadrhy-Sridhar F, Link P, Cowell W

*Osteoporosis International, 2013, 24, 2907-18*

## MINI-ABSTRACT

This review suggests that several interventions, including simplification of dosing regimens, patient decision aids, electronic prescription, and patient education may improve medication adherence and persistence in patients with osteoporosis. We recommend that promising interventions are subjected to further rigorous evaluation to demonstrate that improved adherence translate to greater benefits.

## ABSTRACT

*PURPOSE:* This study aims to systematically review, critically appraise and identify from the published literature, the most effective interventions to improve medication adherence in osteoporosis.

*METHODS:* A literature search using Medline, EMBASE, Cochrane library and CINAHL was undertaken to identify prospective studies published between January 1, 1999 and June 30, 2012. We included studies on adult users of osteoporosis medications that tested a patient adherence intervention (e.g. patient education, intensified patient care, different dosing regimens) and reported quantitative results of adherence. The Delphi list was modified to assess the quality of studies.

*RESULTS:* Of 113 articles identified, 20 studies fulfilled the inclusion criteria. The most frequent intervention was education (n=11) followed by monitoring/supervision (n=4), drug regimens (n=2), drug regimens and patient support (n=1), pharmacist intervention (n=1) and electronic prescription (n=1). Although patient education improved medication adherence in four studies, two large-scale randomized studies reported no benefits. Simplification of dosing regimens (with and without patient support program) was found to have a significant clinical impact on medication adherence and persistence. Monitoring/supervision showed no impact on medication persistence while electronic prescription and pharmacist intervention increased medication adherence or persistence.

*CONCLUSIONS:* This review found that simplification of dosing regimens, decision aids, electronic prescription or patient education may help to improve adherence or persistence to osteoporosis medications. We identified wide variation of quality of studies in the osteoporosis area. The efficacy of patient education was variable across studies, while monitoring/supervision does not seem an effective way to enhance medication adherence or persistence.

## KEY WORDS

Adherence, osteoporosis, intervention, persistence.

## INTRODUCTION

Sub-optimal adherence and persistence with appropriately prescribed medication are prevalent in osteoporosis. Several studies have demonstrated that between 50-75% of patients who were prescribed anti-osteoporotic medications have discontinued their medications within one year [1-5].

Low medication adherence leads to lower gains in bone mineral density and higher fracture rates [6], resulting in substantial clinical and economic burden [7, 8]. Approximately 50% of the potential clinical benefits of osteoporosis medications may be lost due to poor adherence, [7, 9] and the cost-effectiveness of osteoporosis management is significantly affected by reduced medication adherence [10, 11].

There are many strategies aimed at improving adherence and persistence with medications. However, evidence across multiple treatments for a diverse range of diseases, suggests that the effectiveness of current methods is both variable and modest [12, 13]. With specific reference to osteoporosis, there have been several interventions and programs developed in recent years, probably in response to the increasing use of bisphosphonates, first introduced around 1990 [14]. This study aims to critically appraise the published literature on interventions to improve patient adherence and persistence with medications to treat osteoporosis and to determine the most effective interventions. A previous review [15] noted a lack of effective intervention in a small sample of eight studies. Since then, more interventions have been tested and published, and this review provides further examination of interventions to improve adherence and persistence in osteoporosis.

## METHODS

### *SEARCH STRATEGY*

A literature search undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org/) was carried out in Medline, EMBASE, Cochrane library and Cumulative Index to Nursing and Allied Health Literature (CINAHL) and using the following key words separated by Boolean operators: [osteoporosis, low bone density, bone fragility, fractures bone, bone demineralization, pathologic osteopenia, low bone mineral density, low bone mass, low bone turnover, low bone mass density OR bisphosphonates, diphosphonates, etidronic acid, clodronic acid, pamidronicate, risedronate acid, ibandronic acid, alendronate, calcium, colecalciferol, estrogens, hormone replacement therapy (HRT), raloxifene, vitamin D] AND [medication adherence, patient compliance, persistence, non-compliance, non-persistence, concordance, non-concordance], AND [interventions, clinical trial, experiment, RCT]. The search period was from January 1, 1999 to June 30, 2012. We restricted our search to the last decade because as no adherence intervention for use in osteoporosis was identified before that period [15]. References of selected articles and of a prior review [15] were also searched.

### *SELECTION CRITERIA*

We included interventional studies of adult users of osteoporosis medications (not limited to bisphosphonates) or calcium and vitamin D supplements that tested any intervention for an

improvement in adherence or persistence and reported quantitative measures of adherence and/or persistence. Non-English studies or observational studies were excluded.

*EXTRACTED INFORMATION*

Each paper was reviewed independently by two investigators (MH, MS, DH, PL, EM or FGS) and disagreements were resolved by consensus. The extracted information included study design, type of intervention, other characteristics of intervention, measurement of adherence, persistence, outcomes, population, follow-up time, ethics approval, sample size, statistical analysis, results of the intervention effect, medication possession ratios or other adherence or persistence measures, adjustment for confounders and clinical outcomes. Due to the heterogeneity in the methods of adherence measurement and of study outcomes, the analysis was focused on a qualitative assessment.

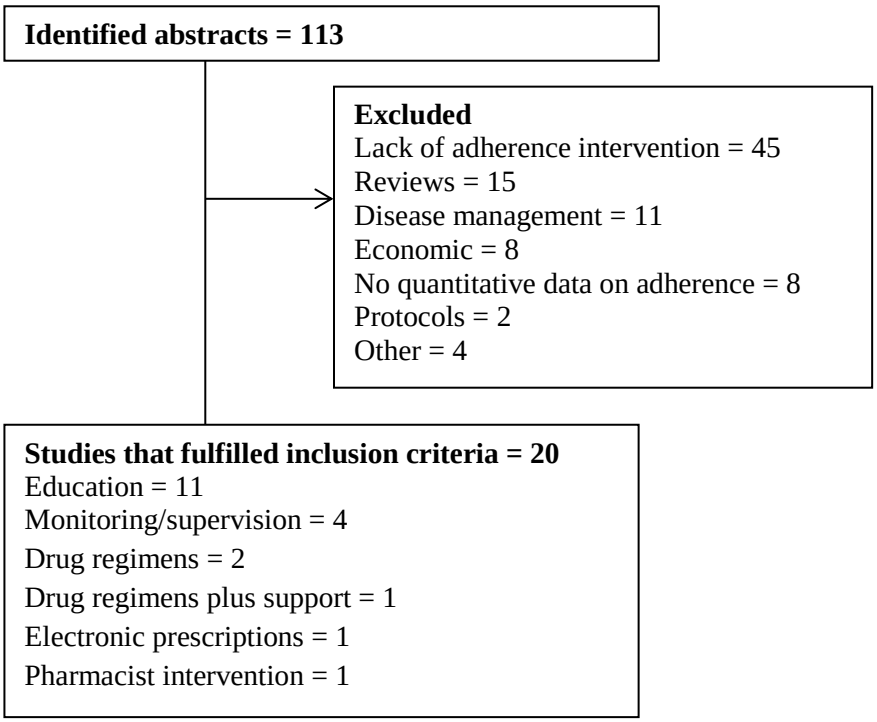
*QUALITY CRITERIA*

The Delphi list [16] was modified to assess the quality of studies. The original checklist contains 17 domains and 8 items but elements to evaluate interventional behavioral studies were not included. Therefore, we added methodological items that were considered relevant for behavioral studies, and they included study design, type of intervention, measure of adherence, outcomes, population, follow-up time, ethics approval, sample size, statistical analysis and results. We assigned a score of 1 if the study included the required item, otherwise zero. Therefore, the maximum score for an article that included all information related to study design, data collection, analysis and interpretation of results was 30 (Appendix 1). Consistency of quality scoring was achieved by having at least two reviewers scoring each paper independently. Only few discrepancies became evident and these were resolved by consensus.

## RESULTS

There were 113 articles identified, and a total of 20 studies [17-36] fulfilled the inclusion criteria (Figure 1). Literature reviews (n=15), research that lacked a medication adherence intervention (n=45), disease management (n=11), economic studies (n=8), descriptions of protocols (n=2), and 4 other were excluded. The most frequent intervention was education (n=11) followed by monitoring/supervision (n=4), simplification of dosing regimens (n=2), drug regimen combined with patient support (n=1), electronic prescriptions (n=1) and pharmacist intervention (n=1). Interventions were led by physicians (n=5), pharmacists (n=4), nurses (n=3), multidisciplinary teams (n=3), clinical personnel (n=3), health educators (n=1) and it was unknown in one study.

**Figure 1**| *Flow diagram of studies*




The characteristics of included studies are reported in Tables 1 and 2. Eleven out of the twenty studies [21, 22, 28-36] were published since 2010. Fifteen studies were randomized controlled trials [18, 20, 21, 24-27, 29-36] and two were cross-over designs. Other studies were non-randomized uncontrolled studies [17, 19, 22, 23, 28]. Most tested an educational program, but these varied substantially between studies [17, 19, 21-24, 27, 28, 31, 35, 36] in the content and method of delivery, which included: group-based, face-to-face, telehealth program, or telephone counseling and written information (letters, leaflets, brochures). In one study [28], pharmacists led the intervention in decentralized clinical-pharmacy managed services. Patients included in the studies were mainly postmenopausal women with osteoporosis. In total, 14,662 patients were included in the studies; 9,420 in the intervention arm and 5,242 in the control arm; 64% of which were from four trials of more than 1,000 patients per trial [20, 24, 25, 35]. Most studies reported ethics review approval, and the follow-up after conduct of the intervention ranged from 4 to 48 months.

**Table 1**| *Characteristics of studies identified which tested a patient adherence and/or persistence intervention*

| References | Design | Interventions / Description / Lead by | Population (inclusion criteria) / drug(s) being assessed | N intervention / control | Planned follow-up |
|---|---|---|---|---|---|
| Blalock et al. (2002) [17] | Non randomized non-controlled trial | Patient education / 1st intervention: tailored educational intervention delivered to individuals (written materials and telephone counseling session). 2nd intervention included the Osteoporosis resource center, workshop and free bone density screening / Not stated | Women / Calcium | 714 / 0 | 1 year |
| Clowes et al. (2004) [18] | Randomized controlled trial | Monitoring / Arm A: Patients with nurse at 12, 24 and 36 weeks. Arm B: Idem + information on response to therapy based on BTM measurements / Nurses | Subjects with osteopenia at either the spine or hip / Raloxifene | 24 and 25 (Arm A and B) / 24 | 1 year |
| Cook et al. (2007) [19] | Non randomized non-controlled trial | Patient education / Telehealth program using motivational interviewing and cognitive–behavioral techniques / Nurses | Patients who received a prescription for risedronate | 402 / 0 | 6 months |
| Cooper et al. (2006) [25] | Randomized controlled trial | Drug regimens and patient support / Monthly ibandronate tablet and patient support (information on osteoporosis, newsletter at 3 months) / Physicians | Postmenopausal women diagnosed with osteoporosis /Weekly alendronate or monthly ibandronate tablet | 529 / 547 | 6 months |
| Delmas et al. (2007) [20] | Randomized controlled trial | Monitoring / At week 13 and 25, all patients received information about the need to continue treatment. Intervention group received feedback on their response to therapy based on BTM measurements / Physicians | Postmenopausal women diagnosed with osteoporosis / Risedronate | 2302 / 1113 | 1 year |

| | | | | | |
|---|---|---|---|---|---|
| Freemantle et al. (2012) [26] | Randomized (crossover) controlled trial | Drug regimens / Subcutaneous denosumab, 60 mg every 6 month versus oral alendronate, 70 mg once weekly / Clinic personnel | Postmenopausal women diagnosed with osteoporosis / Denosumab or alendronate | 106 (denosumab) / 115 (alendronate)* | 24 months |
| Guilera et al. (2006) [27] | Randomized controlled trial | Patient education / Educational leaflet with general information about osteoporosis, and attending physician spent 15 min reviewing the contents of the leaflet with each participant / Physicians | Postmenopausal women diagnosed with osteoporosis / Raloxifene | 366 / 379 | 12 months |
| Heilmann et al. (2012) [28] | Non-randomized controlled trial | Pharmacist-directed intervention / Decentralized clinical-pharmacy-based osteoporosis management service / Pharmacists | Women with a diagnosis code for a fracture / Osteoporosis medications | 291 / 71 | 12 months |
| Hill et al. (2010) [29] | Randomized controlled trial | Electronic prescription / Electronic prescription for the calcium carbonate product with the Electronic medical record system / Physicians | Women between 19 and 50 years old, who attended a general obstetrics and gynecology practice / Calcium | 123 / 122 | 6 months |
| Kendler et al. (2011) [30] | Randomized (crossover) controlled trial | Drug regimens / Subcutaneous denosumab, 60 mg every 6 month versus oral alendronate, 70 mg once weekly / Clinic personal | Postmenopausal women diagnosed with osteoporosis / Denosumab or alendronate | 126 (denosumab) / 124 (alendronate)* | 12 months |
| Lai et al. (2011) [31] | Randomized controlled trial | Patient education and counseling / Participants received counseling on osteoporosis, risk factors, lifestyle modifications, goals of therapy, side effects and the importance of adherence / Pharmacists | Postmenopausal women diagnosed with osteoporosis / Weekly alendronate or risedronate | 100 / 98 | 12 months |
| Montori et al. (2011) [32] | Randomized controlled trial | Patient education and shared-decision making / Patients received the osteoporosis choice decision aid / Physicians | Postmenopausal women with osteoporosis or osteopenia / Bisphosphonates | 52 / 48 | 6 months |

| | | | | | |
|---|---|---|---|---|---|
| Nielsen et al. (2010) [21] | Randomized controlled trial | Patient education and information / Group-based education program, i.e. “school” group (12 hour) / Multidisciplinary team | Patients diagnosed with osteoporosis / Osteoporosis medications | 300 / 150 | 2 years |
| Ojeda-Bruno et al. (2010) [22] | Non randomized non-controlled trial | Patient education / 2 hour education session / Nurses and physicians | Adults older than 50 years of age with a fragility fracture / Bisphosphonates | 380 / 0 | 4 years |
| Robbins et al. (2004) [23] | Non randomized non-controlled trial | Patient education / Teaching about osteoporosis, estrogen and calcium / Nurses | Some women from the on-going 3 year low-dose estrogen study | 109 / 0 | 1 year |
| Roux et al. (2012) [33] | Cluster randomized controlled trial | Monitoring / Bone marker was given at week 6 visit, together with a standardized message about the change compared to baseline / Physicians | Postmenopausal women with osteoporosis / Oral ibandronate | 249 / 343 | 12 months |
| Shu et al. (2009) [24] | Randomized controlled trial | Patient and physician education / Physicians learned specific teaching techniques while patients received letters and automated telephone calls / Trained pharmacists (for physicians) | Participants from the parent trial and at risk for osteoporosis / Osteoporosis medications | 1867 patients and 436 GPs / 875 patients | 10 months |
| Silverman et al. (2012) [34] | Randomized controlled trial | Monitoring and education / (A) bone marker results at baseline, 3 and 12 months; (B) educational materials every month and a membership in the National Osteoporosis Foundation; (C) bone marker and educational information / Study personnel or primary care provider | Postmenopausal women with osteoporosis / Oral bisphosphonates | 60 (A) / 60 (B) / 60 (C) / 59 (control) | 12 months |
| Solomon et al. (2012) [35] | Randomized controlled trial | Patient education and counseling / Program of telephone based counseling / Health educators | Individuals newly prescribed a medication for osteoporosis / Osteoporosis medications | 1046 / 1041 | 12 months |
| Yuksel et al. (2010) [36] | Randomized controlled trial | Screening and patient education / Tailored education program on aspects of osteoporosis / Pharmacists | Patients with osteoporosis / Calcium | 129 / 133 | 4 months |

** Per protocol Analysis*

Table 2 presents primary outcomes, method of adherence measurement, statistical analysis, results, and quality score. All studies used adherence as primary outcome except one study [20] that only reported persistence and two studies where adherence was used as a secondary outcome (persistence being the primary outcome) [28, 36]. Eight studies reported both adherence and persistence data [18, 24-26, 30-32, 35]. Adherence definitions varied: where an explicit cut-off was used to define adherence (e.g. >80% of doses taken), this was applied to calculate the proportion of patients adhering to therapy at time T, proportion of patients taking their medicine correctly, medication possession ratio. In other cases, patients were labeled as adherent without an explicit cut-off. Persistence was defined as the proportion of patients continuing treatments at a given follow-up time. Adherence and persistence outcome data were collected from prescription records (n=7), electronic monitoring (n=5), self-report questionnaire (n=6) and two did not provide the information [17, 33]. None of the studies examined adherence or persistence in relation to clinical outcomes. Eight studies had adjustments for some potential confounders [20, 21, 25, 26, 30, 31, 34, 35] which may not be necessary in properly randomized trials where confounding variables would presumably be distributed evenly across the arms of the trial. Sixteen studies described the characteristics of patients lost during follow-up [7, 18-23, 25-27, 30-32, 34, 35].

**Table 2**| *Continuation of studies identified which tested a patient adherence and/or persistence intervention*

| References | Measures method | | Statistical analysis | | | Results | Quality score |
|---|---|---|---|---|---|---|---|
| | **Outcome(s)** | **Assessment method** | **Statistical method** | **Losses of patients to follow-up taken into account** | **Adjustment for confounders** | | |
| Blalock et al. (2002) [17] | Adherence to calcium intake but no explicit definition | No information | Not reported | No | No | Calcium intake increased of 500 mg/d in the intervention group. | 16/30 |
| Clowes et al. (2004) [18] | Adherence was the proportion of patients adhering to therapy (>75%) at 1 year | Electronic monitoring devices | Kaplan-Meier survival curves | Yes | No | Arm A: 63% (95% CI 43%, 82%)<br>Arm B: 68% (49%, 86%)<br>Control: 42% (22%, 62%)<br>P = 0.15 (Arm A) and 0.05 (Arm B) | 24/30 |
| | Persistence was defined as continuing to take tablets for more than 7 of any 14 days immediately before the 1 year visit | | | | | Monitored group: 84% (74%, 94%)<br>Control: 67% (54%, 87%)<br>P = 0.06 (Arm A) and 0.26 (Arm B) | |
| Cook et al. (2007) [19] | Adherence (percentage of patients still adherent at 6 months) but no explicit definition | Pharmacy fill records | Not reported | Yes | No | Intervention: 69%<br>Control (unpublished national data): 41%<br>P < .001<br>Effect size: 0.19 | 19/30 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cooper et al. (2006) [25] | Persistence (percentage of patients still persistent at 6 months)<br>was defined using discontinuation of at least 1-month without any medication available | Prescription filling | Kaplan-Meier survival curves | Yes | Yes | Intervention: 56.6%<br>Control: 38.6%<br>Hazard ratio = 0.54 (0.44-0.66)<br>P < 0.0001 | 24/30 |
| | Adherence was defined as the proportion of patients who had at least five of the six prescriptions | | | | | Intervention: 80.2%<br>Control: 73.3%<br>P = 0.008 | |
| Delmas et al. (2007) [20] | Persistence at one year | Electronic monitoring | Kaplan-Meier survival curves | Yes | Yes | Intervention: 80%<br>Control: 77%<br>P = 0.16 | 25/30 |
| Freemantle et al. (2012) [26] | Adherence was defined as the proportion of patients who were both compliant and persistent to treatment. | Medication event monitoring system | Cochran–Mantel–Haenszel test | Yes | Yes | Non-adherence with denosumab (2nd year): 7.5%<br>Alendronate: 36.5%<br>Risk ratio = 0.20<br>P < 0.001 | 28/30 |
| | Persistence was defined as the proportion persisting with treatment after crossover | | | | | Denosumab: 97.2%<br>Alendronate: 72.6%<br>Risk ratio = 0.09<br>P < 0.001 | |
| Guilera et al. (2006) [27] | Adherence was assessed using the Morisky test (four questions) | Self-completed questionnaire | Student t test and Mann Whitney test | Yes | No | Intervention: 52.5%<br>Control: 47.4%<br>P = 0.38 | 21/30 |
| Heilmann et al. (2012) [28] | Adherence was defined as the proportion of patients who had a medication possession ratio of at least 80% | Pharmacy databases | Chi-square analysis | No | No | Intervention: 46%<br>Control: 28%<br>P = 0.007 | 18/30 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hill et al. (2010) [29] | Proportion of women who reported calcium intake at 6 months | Telephone survey | Chi-square analysis and *t* tests | No | No | Intervention: 57.0%<br>Control: 26.5%<br>RR = 2.2 (1.5–3.1)<br>P = 0.001 | 25/30 |
| Kendler et al. (2011) [30] | Adherence was defined as the proportion of patients who were both compliant and persistent to treatment at the end of treatment period. | Medication event monitoring system | Cochran–Mantel–Haenszel test | Yes | Yes | Denosumab: 87.3%<br>Alendronate: 76.6%<br>Risk ratio = 0.58<br>P = 0.043 | 28/30 |
| | Persistence was defined as the proportion persisting with treatment at the end of treatment period | | | | | Denosumab: 89.7%<br>Alendronate: 79.8%<br>Risk ratio = 0.54<br>P = 0.049 | |
| Lai et al. (2011) [31] | Adherence is defined as the average<br>percentage of participants who were both persistent and compliant | Pill count and self -report | Mann-Whitney U test | Yes | Yes | Self-report: higher adherence in the intervention group (98.9% vs. 96.8%; P = 0.015 at 6 months); (98.0% vs. 96.2%; P = 0.047 at 12 months)<br>Pill count: 98.8% vs. 97.0%; P = 0.028 (6 months) and 97.7% vs. 96.5%; P=0.32 (12 months) | 27/30 |
| | Persistence was the percentage of patients who continued bisphosphonate at 12 months | Prescription filling | Kaplan-Meier survival curves and log rank test | | | Intervention: 89.8%<br>Control: 87.0%<br>P = 0.481 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Montori et al. (2011) [32] | Adherence was defined as the proportion of patients who had 80% or greater adherence to bisphosphonates | Self-report (telephone survey) and pharmacy fill records | Wilcoxon rank-sum tests | Yes | No | Intervention: 23 patients<br>Control: 14 patients<br>P = 0.009 | 22/30 |
| | Persistence was measured as the number of days covered | | | | | Intervention: 170 days<br>Control: 180 days<br>P = 0.38 | |
| Nielsen et al. (2010) [21] | Adherence was defined as patients taking their medicine correctly at the appropriate time. An explicit definition was not provided | Self-completed questionnaire | Kaplan-Meier survival curves | Yes | Yes | Intervention: 92%<br>Control: 80%<br>P = 0.006 | 25/30 |
| Ojeda-Bruno et al. (2010) [22] | Adherence with treatment but no clear definition | Self-report (telephone survey) | No statistical analysis | Yes | No | Intervention: 71% | 15/30 |
| Robbins et al. (2004) [23] | Adherence but no explicit definition | Pill counts and electronic monitoring | Not reported | Yes | No | Baseline: 95% (SD 1.7)<br>12-months: 96% (SD 1.8) | 15/30 |
| Roux et al. (2012) [33] | Persistence was defined as the proportion patients still treated at the last visit, and having taken at least 10 out of 12 pills | Not reported | Chi-square analysis | Yes | No | Persistence at one year:<br>Intervention: 75.1%<br>Control: 74.8%<br>P = 0.932 | 22/30 |
| Shu et al. (2009) [24] | Adherence was expressed as medical possession ratio | Prescription filling | Poisson distribution regression analysis | NR | No | Intervention: 74% (19%, 93%)<br>Control: 73% (0%, 93%)<br>P = 0.18 | 20/30 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Persistence was expressed as median days until discontinuation, where discontinuation was defined as at least 30 days without any medication available | | | | | Interventions: 85 days (58, 174 days)<br>Control: 79 days (31, 158 days)<br>P = 0.16 | |
| Silverman et al. (2012) [34] | Persistence was defined as patients who refilled their prescription | Prescription filling | Survival analysis | Yes | Yes | RR group1/control: 1.09 (p>0.97.<br>RR group 2/ control: 0.95 (p>0.91).<br>RR group 3/control: 1.18 (p>0.23). | 22/30 |
| Solomon et al. (2012) [35] | Adherence was expressed as medication possession ratio | Prescription filling | Kruskal-Wallis test | Yes | Yes | Intervention: 49%<br>Control: 41%<br>P = 0.07 | 24/30 |
| | Persistence was defined as days from initial prescription until the first period during which the patient experienced an interruption in prescription filling lasting longer than 60 days | | Kaplan-Meier survival curves and log rank test | | | P = 0.34 | |
| Yuksel et al. (2010) [36] | Calcium intake at the end of 16 weeks | During a pharmacy visit | Frequencies and chi-square analyses | Yes | No | Patients reaching total daily calcium of 1,500 mg (diet + supplement):<br>Intervention: 30%<br>Control: 19%<br>RR = 1.6 (1.0–2.5).<br>P = 0.011 | 24/30 |

*NR Not reported, RR relative risk*

Among studies including a control group (n=16), twelve reported data on adherence [18, 19, 21, 24-28, 30-32, 35]. In studies where adherence was defined as percentage of patients adherent [18, 21, 24-28, 30, 31, 35], the adherence ranged from 46% to 92% with the intervention while in the control group it varied from 28% to 87%. Nine studies showed a statistically significant (p=0.05) improvement in medication adherence by the intervention compared to the control group [18, 19, 21, 25, 26, 28, 30-32]. Clowes et al. [18] showed that patients receiving feedback information in response to therapy based on bone turnover marker measurements experienced an improved adherence. Monitoring increased cumulative adherence in this study by 57% compared with no monitoring (P=0.004). Patient education and information were found to have a significant impact on medication adherence in two small studies [19, 21], but this result was not confirmed by two large-scale randomized studies [24, 35]. The use of a decision aid had a significant impact on the number of adherent patients (23 patients vs. 14 patients, p = 0.009) [32], and pharmaceutical care was shown to improve adherence in two studies [28, 31] although, in one of these, a significant improvement was only found using self-report questionnaire and not using pill count [31]. The simplification of dosing regimens was shown to significantly influence medication adherence. Cooper et al. showed that once-monthly ibandronate treatment plus a patient support program significantly increased medication adherence compared to once-weekly alendronate [25], while a subcutaneous injection of denosumab every 6 months was shown to significantly improve adherence compared with weekly oral alendronate [26, 30].

Among the thirteen studies assessing the impact of intervention on persistence [18, 20, 24-26, 29-36], only five showed a positive impact of the intervention [25, 26, 29, 30, 36]. Simplification of dosing regimens was found to have a significant impact on medication persistence [25, 26, 30]. Patients were most persistent with those having the least frequent dosing regimens. Electronic prescription also increased persistence with calcium (57% vs. 22%, study vs. control groups, p = 0.001) [29] and education by pharmacists increased calcium intake at 4 months (30% vs. 19%, study vs. control groups, p = 0.011). None of the four studies assessing monitoring/supervision intervention showed an impact on persistence [18, 20, 33, 34] and most education programs had no significant impact on persistence [24, 31, 35], including the patient support program [32].

The quality of the studies was variable with an average quality score of 74% (range from 50% to 93%). Improved quality scores were obtained in more recent studies with an average quality score increasing from 66% to 80% for studies published before and after 2010, respectively.

## DISCUSSION

We reviewed studies that assessed interventions designed to enhance patient adherence and persistence to osteoporosis medications. This study considered new interventions to previous

reviews [15]. Some of these provided further evidence on the impact of patient education and monitoring/supervision on medication adherence while others tested new interventions or programs. From our update, it emerged that the efficacy of patient education is still uncertain. Nielsen et al. [21] reported an improvement in adherence but a large-scale randomized trial found no statistically significant improvement in adherence of a telephonic motivational interviewing intervention [35]. A large well conducted RCT is definitive within the study context, but perhaps not generalizable to all forms of education. Other studies [33, 34] confirmed that monitoring and providing feedback to patients on bone marker results is not an effective way to enhance persistence and adherence. New interventions being tested suggested that less frequent dosing regimens [26, 30], electronic prescription [29] and patient decision aids to facilitate decision-making by describing the available options [32] could be effective patient-focused intervention to improve adherence and persistence.

The existing literature on interventions to improve patient adherence and persistence has several limitations. First, studies were of limited quality - only 15 studies were randomized trials and only one of the studies was a double-blinded trial. While an improvement in the quality of studies was observed over time, well-designed randomized controlled trials are needed to assess the efficacy of enhancing adherence to osteoporosis medications. We acknowledge, however, that conducting a doubled-blind trial for testing an intervention for improving adherence and persistence may be difficult and sometimes impossible (e.g. blinding participants to an educational intervention). However, the use of cluster randomized controlled trials could be one way to mitigate specific methodological constraints. Second, the definitions and measurement of medication adherence and persistence were inconsistent, precluding any quantitative synthesis of the evidence. The International Society for Pharmacoeconomics & Outcomes Research (ISPOR) has previously provided guidance on how to conduct research on medication adherence using both retrospective and prospective designs [37, 38]. A new taxonomy for describing and defining adherence to medications was also recently published by the ABC project team [39], which may facilitate standardization of future research. Adherence to medication is defined as “the process by which patients take their medication as prescribed” and persistence to medication as “the time from initiation until discontinuation” [39]. Third, information reported by authors of each article was limited. Where mean adherence scores were provided for RCTs, no information was available on the standard deviations, making it difficult to calculate a standardized effect size, which could be used as a comparative measure across studies. There was limited information reported on specific relevant points including the extent of patient co-payments, and setting of care (i.e. at research centers or within the community). Fourth, no studies examined the impact of the interventions on clinical outcomes. Although testing for efficacy using proxy outcomes (e.g. adherence) is informative, it would also be appropriate for future studies to assess clinical outcomes (e.g. fractures) alongside persistence and adherence. Finally, the durability of intervention effect, and

appropriate period of follow-up are important considerations which are largely overlooked. Osteoporosis is a chronic disease requiring long-term treatment. A single intervention is unlikely to yield anything more than transient improvements in adherence. Increased treatment effectiveness is most probable with repeated administration of interventions, and can only be demonstrated with long-term follow-up of patients, greater than 1 year.

Problems with internal and external validity of the presented data, and potential biases, could also limit the usefulness of some studies. Non-randomized uncontrolled trials [17, 19, 22, 23, 28] are prone to non-equivalent patient characteristics at the beginning of the study and differential rates of patient drop-out during follow-up. This reduces internal validity, as does the confounding effect of time in studies that adopt a pre-post group research design. External validity could also be uncertain since samples may not be wholly representative of populations with osteoporosis [17]. Measurement bias may also have occurred in those studies that used only measures of self-report to determine adherence [21, 22, 27]. It could also occur in those studies where there was lack of blinding between the data analysts and treatment groups involved. Lack of appropriate training of staff in the use of tools could lead to an undermining of the interventions' fidelity.

There were potential issues in relation to the methodology and execution of the review. While only one person conducted the literature search, it was undertaken as comprehensively as possible using multiple search terms, increasing confidence that all relevant studies were identified. The quality score was used to ensure consistency in the way we evaluated papers, with only a few discrepancies observed between reviewers which were only a matter of interpretation. Since the interventions varied across studies, we presented the information by study, and by broad intervention category. So, if an intervention was focused on educating patients using different tools, we did not focus on the tools, we grouped them as "educational intervention". Adherence is a multifactorial problem, and therefore, there is no single intervention that works across different individuals' needs. We proposed to compare different intervention types and try to identify if there were clear differences among them. We would expect to update our review when new relevant interventions become available, especially with advances in telehealth technology and social media.

In summary, this review indicates that several interventions (simplification of dosing regimens, electronic prescription, patient decision aids or patient education) may improve adherence and persistence to medicines for osteoporosis, although, there were variations in the quality of studies. Of the largest and least biased studies, patient education showed however only marginal improvement in medication adherence and persistence, while monitoring/supervision seems ineffective in enhancing medication adherence. To demonstrate the societal benefits of adherence improvement, we recommend that the most promising interventions are subjected to rigorous evaluation of clinical effectiveness in pragmatically-designed, randomized, controlled trials. It may be necessary to target interventions to specific causes of non-adherence, in an approach consistent

with personalized medicine, in acknowledgment that the average effect from trials masks some patients who are very responsive to interventions.

## ACKNOWLEDGEMENTS

This article is written by members of the International Society for Pharmacoeconomics & Outcomes research (ISPOR) Medication Adherence & Persistence Special Interest Group. The authors have no conflicts of interest relevant to the content of this study.

## REFERENCES


1. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006;38(6):922-8.
2. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int. 2010;21(11):1943-51.
3. Rabenda V, Hiligsmann M, Reginster J-Y. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. Expert Opin Pharmacother. 2009;10(14):2303-15.
4. Rabenda V, Mertens R, Fabri V, Vanoverloop J, Sumkay F, Vannecke C, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int. 2008;19(6):811-8.
5. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc. 2006;81(8):1013-22.
6. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RMC, Silverman SL. Impact of treatment adherence on fracture rates in North America and Europe. Am J Med. 2009;122(2 Suppl):S3-13.
7. Hiligsmann M, Rabenda V, Bruyere O, Reginster JY. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy. 2010;96(2):170-7.
8. Landfeldt E, Lundkvist J, Strom O. The societal burden of poor persistence to treatment of osteoporosis in Sweden. Bone. 2011;48(2):380-8.
9. Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. Value Health. 2012;15(5):604-12
10. Hiligsmann M, Gathon HJ, Bruyere O, Ethgen O, Rabenda V, Reginster JY. Cost-Effectiveness of Osteoporosis Screening Followed by Treatment: The Impact of Medication Adherence. Value Health. 2010;13(3):394-401.
11. Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY. Potential Clinical and Economic Impact of Nonadherence with Osteoporosis Medications. Calcif Tissue Int. 2010;86(3):202-10.
12. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. JAMA. 2002;288(22):2868-79.
13. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2008;(2):CD000011.
14. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med. 1990;322(18):1265-71.
15. Gleeson T, Iversen MD, Avorn J, Brookhart AM, Katz JN, Losina E, et al. Interventions to improve adherence and persistence with osteoporosis medications: a systematic literature review. Osteoporos Int. 2009;20(12):2127-34.
16. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 1998;51(12):1235-41.

17. Blalock SJ, DeVellis BM, Patterson CC, Campbell MK, Orenstein DR, Dooley MA. Effects of an osteoporosis prevention program incorporating tailored educational materials. Am J Health Promot. 2002;16(3):146-56.
18. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab. 2004;89(3):1117-23.
19. Cook PF, Emiliozzi S, McCabe MM. Telephone counseling to improve osteoporosis treatment adherence: an effectiveness study in community practice settings. Am J Med Qual. 2007;22(6):445-56.
20. Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2007;92(4):1296-304.
21. Nielsen D, Ryg J, Nielsen W, Knold B, Nissen N, Brixen K. Patient education in groups increases knowledge of osteoporosis and adherence to treatment: a two-year randomized controlled trial. Patient Educ Couns. 2010;81(2):155-60.
22. Ojeda-Bruno S, Naranjo A, Francisco-Hernandez F, Erausquin C, Rua-Figueroa I, Quevedo JC, et al. Secondary prevention program for osteoporotic fractures and long-term adherence to bisphosphonates. Osteoporos Int. 2011;22(6):1821-8.
23. Robbins B, Rausch KJ, Garcia RI, Prestwood KM. Multicultural medication adherence: a comparative study. J Gerontol Nurs. 2004;30(7):25-32.
24. Shu AD, Stedman MR, Polinski JM, Jan SA, Patel M, Truppo C, et al. Adherence to osteoporosis medications after patient and physician brief education: post hoc analysis of a randomized controlled trial. Am J Manag Care. 2009;15(7):417-24.
25. Cooper A, Drake J, Brankin E. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. Int J Clin Pract. 2006;60(8):896-905.
26. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int. 2012;23(1):317-26.
27. Guilera M, Fuentes M, Grifols M, Ferrer J, Badia X. Does an educational leaflet improve self-reported adherence to therapy in osteoporosis? The OPTIMA study. Osteoporos Int. 2006;17(5):664-71.
28. Heilmann RM, Friesleben CR, Billups SJ. Impact of a pharmacist-directed intervention in postmenopausal women after fracture. Am J Health Syst Pharm. 2012;69(6):504-9.
29. Hill DA, Cacciatore M, Lamvu GM. Electronic prescribing influence on calcium supplementation: a randomized controlled trial. Am J Obstet Gynecol. 2010;202(3):236 e1-5.
30. Kendler DL, McClung MR, Freemantle N, Lillestol M, Moffett AH, Borenstein J, et al. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. Osteoporos Int. 2011;22(6):1725-35.
31. Lai PS, Chua SS, Chew YY, Chan SP. Effects of pharmaceutical care on adherence and persistence to bisphosphonates in postmenopausal osteoporotic women. J Clin Pharm Ther. 2011;36(5):557-67.

32. Montori VM, Shah ND, Pencille LJ, Branda ME, Van Houten HK, Swiglo BA, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. Am J Med. 2011;124(6):549-56.
33. Roux C, Giraudeau B, Rouanet S, Dubourg G, Perrodeau E, Ravaud P. Monitoring of bone turnover markers does not improve persistence with ibandronate treatment. Joint Bone Spine. 2012;79(4):389-92.
34. Silverman SL, Nasser K, Nattrass S, Drinkwater B. Impact of bone turnover markers and/or educational information on persistence to oral bisphosphonate therapy: a community setting-based trial. Osteoporos Int. 2012;23(3):1069-74.
35. Solomon DH, Iversen MD, Avorn J, Gleeson T, Brookhart MA, Patrick AR, et al. Osteoporosis telephonic intervention to improve medication regimen adherence: a large, pragmatic, randomized controlled trial. Arch Intern Med. 2012;172(6):477-83.
36. Yuksel N, Majumdar SR, Biggs C, Tsuyuki RT. Community pharmacist-initiated screening program for osteoporosis: randomized controlled trial. Osteoporos Int. 2010;21(3):391-8.
37. Gwadry-Sridhar FH, Manias E, Zhang Y, Roy A, Yu-Isenberg K, Hughes DA, et al. A framework for planning and critiquing medication compliance and persistence research using prospective study designs. Clin Ther. 2009;31(2):421-35.
38. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. Value Health. 2007;10(1):3-12.
39. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012;73(5):691-705.

## APPENDIX 1. MODIFIED VERSION OF THE DELPHI LIST

| Domains | Original Delphi List | Modified List |
|---|---|---|
| 1. Study question | | Was the research question/objective/hypothesis or aim clearly described<br>Yes (1)/ No (0) |
| 2. Population | Were the eligibility criteria specified?<br>Yes/No/Don't know | Were inclusion criteria clearly described?<br>Yes (1)/No (0)<br>Were exclusion criteria clearly described?<br>Yes (1)/No (0) |
| 3. Sample size and power Calculations a priori | | Was sample size and power calculated a priori?<br>Yes (1)/ No (0)<br>Were the total number of individuals, the total number of participants in the study group and total number of patients in the controlled group clearly specified?<br>Yes (3, one per each)/ No (0) |
| 4. Treatment allocation | a) Was a method of randomization performed?<br>Yes/No/Don't know<br>b) Was the treatment allocation concealed?<br>Yes/No/Don't know | Was randomization used in the study<br>Yes (1)/ No (0) |
| 5. Confounders | | Were potential confounders clearly described?<br>Yes (1)/No (0) |
| 6. Ethics | | Was the protocol approved by the Ethics Committee and/or patients signed informed consent?<br>Yes (1)/No (0) |
| 7. Intervention | | Was intervention clearly defined?<br>Yes (1)/No (0)<br>Was the intervention clearly described (who did what, to whom, where and how often)?<br>Yes (1)/No (0) |
| Comparator | | Was a comparator included in the study?<br>Yes (1)/No (0)<br>Was comparator clearly described?<br>Yes (1)/No (0) |

| | | |
|---|---|---|
| 8. Outcome measures | | Was (were) measure (s) of adherence defined?<br>Yes (1)/No (0)<br>Was (were) measure (s) of adherence clearly described in the study?<br>Yes (1)/No (0)<br>Were clinical outcomes included in the study?<br>Yes (1)/No (0) |
| 9. Follow-up/withdrawals | | Was followed-up time specified in the study?<br>Yes (1)/No (0) |
| 10. Blinding | Was the outcome assessor blinded?<br>Yes/No/Don't know<br>Was the care provider blinded?<br>Yes/No/Don't know<br>Was the patient blinded?<br>Yes/No/Don't know | Was the study:<br>a. Double blind<br>Yes (2)/No (0)<br>b. Single blind<br>Yes (1)/No (0) |
| 15. Analysis | Were the groups similar at baseline regarding the most important prognostic indicators?<br>Yes/No/Don't know<br>Were point estimates and measures of variability presented for the primary outcome measures? Yes/No/Don't know<br>Did the analysis include an intention-to treat analysis? Yes/No/Don't know | Was the statistical method appropriate?<br>Yes (1)/No (0)<br>Was the analysis adjusted by confounders?<br>Yes (1)/No (0)<br>Were losses of patients to follow-up taken into account?<br>Yes (1)/No (0)<br>Were characteristics of patients lost to follow-up clearly described?<br>Yes (1)/No (0) |
| Results | | Were adherence results clearly presented (e.g. baseline, interim, and at the end of the study)?<br>Yes (3)/No (0)<br>Were clinical results clearly presented (e.g. baseline, interim, and at the end of the study)?<br>Yes (1)/No (0)<br>Were results adjusted by confounders?<br>Yes (1)/No (0) |
| 16. External Validity | | Was the included population representative of study population?<br>Yes (1)/No (0) |
| Total | | 30 (100% Quality Score) |

# PART 3

## PREFERENCE STUDIES

CHAPTER 8

# NOMINAL GROUP TECHNIQUE TO SELECT ATTRIBUTES FOR DISCRETE CHOICE EXPERIMENTS. AN EXAMPLE FOR DRUG TREATMENT CHOICES IN OSTEOPOROSIS.

**Hiligsmann M**, van Durme C, Geusens P, Dirksen C, Dellaert B, van der Weijden T, Reginster JY, Boonen A

*Patient Preference & Adherence, 2013, 7, 133-9*

## ABSTRACT

*OBJECTIVES:* Attribute selection represents an important step in the development of discrete-choice experiments (DCE), but is often poorly reported. In some situations, the number of identified attributes may exceed what one may find possible to pilot in a DCE. Hence there is a need to gain insight into methods to select attributes in order to construct the final list of attributes**.** This study aims to test the feasibility of using the nominal group technique (NGT) to select attributes for DCEs.

*METHODS:* Patients group discussions (4-8 participants) were conducted to prioritize a list of twelve potentially important attributes for osteoporosis drug therapy. The NGT consisted of three steps: (1) an individual ranking of the twelve attributes by importance from 1 to 12, (2) a group discussion on each of the attributes including a group review of the aggregate score of the initial rankings, and (3) a second ranking task of the same attributes.

*RESULTS:* Twenty-six osteoporotic patients participated in five NGT sessions. Most (80%) patients changed their ranking after the discussion. However, the average initial and final ranking did not markedly differ. In the final rank, the most important medication attributes were effectiveness, side-effects, frequency and mode of administration. Some (15%) patients did not correctly rank from 1 to 12, and the order of attributes did play a role in the ranking.

*CONCLUSION:* The NGT is feasible for selecting attributes for DCE. Although, in this study context, the NGT session had little impact on prioritizing attributes, this approach is rigorous, transparent and improves the face validity of DCEs. Additional research in other contexts (different decisional problems or different diseases) are needed to determine the added value of the NGT session, to assess the optimal ranking/rating method with control of ordering effects and to compare the attributes selected with different approaches.



## KEYWORDS

Discrete choice experiment, nominal group technique, patients' preferences, medication attributes, osteoporosis

## INTRODUCTION

Over the last decade, discrete choice experiments (DCEs) have been increasingly used to elicit preferences for health care [1-3]. The identification and selection of attributes are fundamentally important to obtain valuable results [4, 5] but are often poorly reported [5]. Methods used to identify attributes include literature review, discussion with experts, professional recommendations, surveys, in-depth interviews, focus group and repertory grid techniques [5, 6]. This first stage would generate a list of potential attributes for inclusion. In some situations, the number of identified attributes may exceed what one may find possible to pilot in a DCE. When the number of attributes may need to be restricted, the ISPOR Good Research Practices for Conjoint Analysis Task Force has suggested rating and/or ranking exercises may be beneficial to assess the importance of attributes in order to construct the final list of attributes to be included [1]. Some of the earlier techniques can again be used (focus groups, interviews, etc.) but with a different objective from that in the identification stage.

Nominal group technique (NGT) seems especially suitable for the "second" stage in which attributes are selected from the list by ranking them. The NGT is a structured, multi-step, facilitated group meeting technique used to elicit and prioritize responses to a specific question [7]. This method has been shown to be feasible and reliable for prioritizing health and health care research/problems [8, 9], but has never been investigated to select attributes for DCEs.

This study was therefore designed to assess the use of the NGT to prioritize attributes for inclusion in DCE. The study context is preferences for osteoporosis medications among adult patients. With the recent introduction of new therapies, conducting a DCE would be useful to understand patients' preferences for these treatments, especially when realizing poor adherence to drug treatment in osteoporosis, but a DCE requires a rigorous and transparent approach to select attributes as many potential attributes were identified in surveys [10, 11] and prior DCEs [12-14]. While the results provide insight into preferences for the attributes of osteoporosis medications, the primary objective of this paper was to test the feasibility and usefulness of the NGT to select attributes for DCEs. A secondary objective was to assess the influence of attribute ranking order on the selection of attributes.

## METHODS

### *PATIENTS*

Five patients' group discussions (consisting of 4-8 participants per NGT session) were conducted in June 2011 in the Netherlands and in Belgium to prioritize patients' preferences for medication attributes. Patients were recruited during outpatient clinics or by telephone. Participants were considered eligible for inclusion in the study if they were diagnosed with osteoporosis or had a

recent fracture that required osteoporosis medication during at least a period of their osteoporosis history. They were selected to represent the full clinical spectrum of ages, educational level, history of osteoporosis (primary or secondary) and osteoporosis medication (switched, stopped, experienced side-effects). The ethics committee of Maastricht University Medical Center approved the study and all patients received an information letter before participating and provided written consent.

*IDENTIFICATION OF CANDIDATE ATTRIBUTES*

Fourteen potentially important attributes for osteoporosis drug therapy were established from literature review [10-15] and discussions with experts. Two attributes (i.e. treatment duration and drug interactions) were not included in the final list since these attributes did not meet the important conditions of attributes for DCEs such as being capable of being traded and being policy relevant [4, 5]. Indeed, treatment duration does not differ between first-line osteoporosis therapies being therefore not policy relevant and drug interactions are very rare for all drugs in osteoporosis [16]. The final list of 12 attributes (Table 1) was approved by the working group including project investigators (rheumatologists, DCE experts), advisors and a patient. A different ordering to present and discuss the attributes was used in each of the groups. Attributes were randomly divided into 5 sets (attributes 1-3, 4-6, 7-8, 9-10 and 10-11) and each of the 5 discussion groups received a different ordering of these sets.

**Table 1|** *List of potentially important attributes*

1. Efficacy (effect) in reducing the risk of future fractures *(decreasing by between 20-75% of the risk of future fractures)*
2. Side-effects *(mild and common; serious and rare)*
3. Biological mechanism of action *(bone resorption or bone formation)*
4. Frequency of administration *(daily, weekly, monthly, yearly, etc.)*
5. Mode of administration *(oral tablet, subcutaneous, intravenous, etc.)*
6. Place of administration *(at home, doctor's office, hospital, etc.)*
7. Same drug during the treatment period *(or sequential treatment)*
8. Mono therapy vs. combination therapy *(one or two pills)*
9. Out-of-pocket cost *(personal contribution)*
10. Cost for the society *(other healthcare costs than patient contribution)*
11. Time on market *(recently vs. 10 years)*
12. Branded or generic specification

*NOMINAL GROUP PROCESS*

The NGT process consisted of three steps. After being informed about the purpose of the study (*"to determine the most important characteristics for drug therapy in osteoporosis from the perspective of the patients")* and being given a brief description of the NGT process and of the attributes, each participant was asked to rank the list of attributes by importance from 1 (the most important) to 12 (the least important) on a worksheet. Patients had also the opportunity to include any missing attribute. In comparison with a traditional NGT [17], and since many attributes were already identified in the literature, we have not included a first stage of silent generation of ideas where participants are asked to write down all ideas (here attributes) about a question.

During a second step (discussion and sharing ideas), a group discussion on each of the attributes was performed including a group review of the aggregate score of the initial rankings. In the final phase, participants had the opportunity to reconsider their initial ranking in the light of other participants' views. They were under no pressure to achieve consensus, and all ratings were again made privately. The discussions were facilitated by a medical trainee in rheumatology observed by a moderator and tape recorded. The facilitator tried to ensure that all participants were given an opportunity to contribute. NGT sessions were conducted until the rank order of the most important attributes did not change anymore.

For each of the 5 groups, the individual rankings were summed across participants to derive the rank order at the group level. Some recoding was performed for a few patients who assigned the same number to different attributes. Any change between the initial and final round was examined to indicate the impact of the NGT on ranking. This analysis was carried out at the group level and at the individual level by examining the number of attributes changed by responders and the average of the (absolute) change between attribute's rankings.

*FINAL ATTRIBUTES SELECTION*

The selection of attributes for the DCE was based on groups' ranking and NGT discussions followed by experts' discussion who decided on the number of attributes that should be included. The NGT sessions were especially useful to determine the cutoff level after which attribute of the final ranking list, the inclusion should be stopped. The final list of attributes was further approved by the working group. No fixed threshold number was used to select attributes for inclusion although recent reviews have reported that most DCEs used a number of attributes between 4 and 7 [18, 19].

## RESULTS

### *STUDY SAMPLE*

After five group discussions (two in the Netherlands and three in Belgium), the rank order of the attributes did not change anymore and no additional groups were invited. The final sample consisted of 26 osteoporotic patients. As observed on Table 2, patients represented the full clinical spectrum of ages, educational level, osteoporosis diagnosis, fracture history and treatment. Patients' characteristics did not markedly differ between groups.

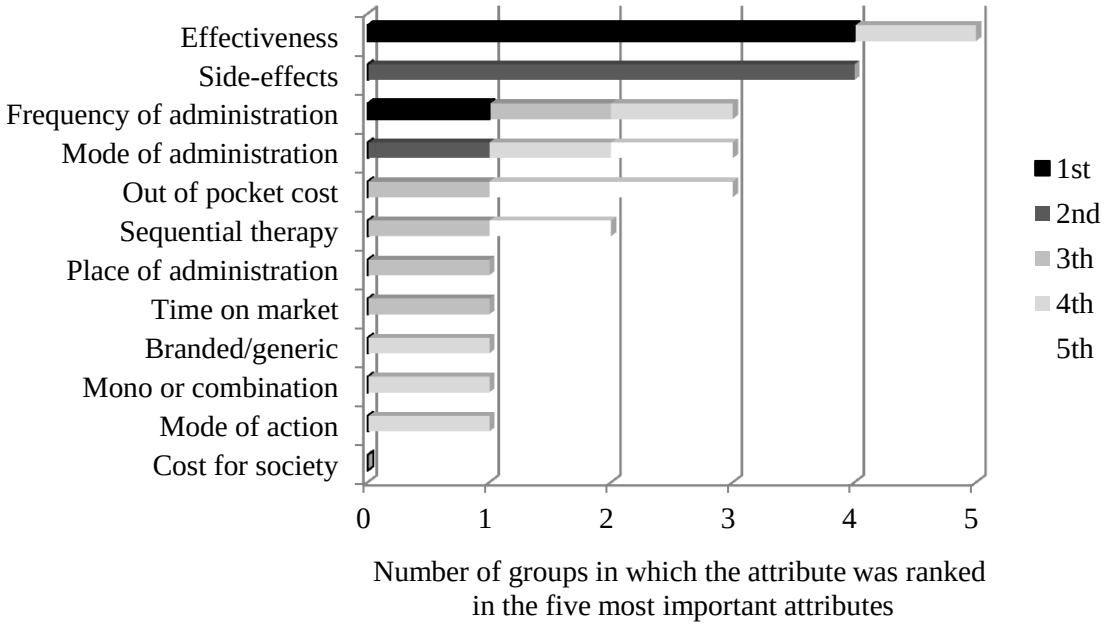
**Table 2|** *Participants' characteristics*

| | |
|---|---|
| Women | 24/26 (92%) |
| Belgian | 17/26 (66%) |
| Age | |
| Mean, median, standard deviation | 68.0, 67.0, 11.0 |
| Range | 41-87 |
| Diagnosis of osteoporosis | 25 (96%) |
| Osteoporosis since | |
| Mean, median, standard deviation | 10.2, 8.0, 8.7 |
| Range | 0-38 |
| Education | |
| No, primary or low secondary | 9 (37%) |
| Secondary school | 9 (37%) |
| Graduate / University | 6 (25%) |
| With prior fracture | 15 (58%) |
| Number of prior fractures | |
| Mean, median, standard deviation | 1.04, 1.00, 1.22 |
| Range | 0-5 |
| Patients on treatment | 25 (96%) |
| Patients who took another treatment in the past | 9 (35%) |
| Patients who experienced adverse events | 4 (15%) |

### *MOST IMPORTANT ATTRIBUTES (FINAL RANKING)*

Figure 1 presents the five most important attributes in the different patients' groups. Drug effectiveness was the most important medication attribute followed by side-effects, frequency of administration and mode of administration, respectively. While out-of-pocket costs, time on market, place of administration (such as hospital, home) and the need for sequential treatment were of some relevance, costs for society, mode of action, combination treatment and brand/generic specification did not reach the top three most important attributes in any of the groups.

**Figure 1**| *Most important attributes for osteoporosis medications*




*EFFECT OF NGT ON RANK ORDER*

Twenty of the 25 patients (80%) who provided an initial and final ranking changed their ranking after the discussion. However, the average initial and final ranking did not differ importantly, with two exceptions (Table 3). The importance of mode of action was reduced after discussions (from position 5 to position 8) while the out-of-pocket costs increased from position 10 to 5 because, in two Belgian groups, the importance of this attribute increased by 3 and 4 places after discussions, respectively. Mode of action was considered by most patients as a way of improving effectiveness and reducing fractures, although drugs' effectiveness is largely independent of the biological mechanism of drugs. This explanation was provided during the NGT discussions, explaining why this attribute was considered less important in the final ranking.

**Table 3|** *Ranking of osteoporosis medication attributes before and after NGT meeting. (The average ranks assigned to each attribute in the five groups are provided in parentheses)*

| | **Initial ranking** | **Final ranking** |
|---|---|---|
| Effectiveness | 1 (2.0) | 1 (1.6) |
| Side-effects | 2 (3.2) | 2 (3.8) |
| Frequency of administration | 3 (5.2) | 3 (4.4) |
| Mode of administration | 4 (5.4) | 4 (5.8) |
| Out of pocket cost | 10 (7.8) | 5 (6.0) |
| Time on market | 6 (6.0) | 6 (6.4) |
| Place of administration | 7 (6.6) | 7 (6.6) |
| Mode of action | 5 (5.8) | 8 (6.8) |
| Sequential therapy | 8 (7.2) | 9 (7.0) |
| Mono or combination | 9 (7.4) | 10 (7.4) |
| Branded/generic | 11 (8.8) | 11 (9.0) |
| Cost for society | 12 (11.6) | 12 (11.8) |

Individual patient analyses have revealed different profiles of respondents (Table 4). Some patients (profile 1) did not change their ranking after discussion, some (profile 2) made minor changes to some parameters and others (profiles 3-4) made more substantial changes in their ranking. After discussion, the average absolute change per patient between the twelve attributes' ranking in the second ranking list compared to the first ranking list was 1.3 (standard deviation: 0.8) meaning that, on average, each attribute moved (in absolute term) by 1.3 place. The average number of attributes changed after discussion was 6.8 (standard deviation: 3.1). As reported on Figure 2, the NGT discussion had the lowest impact on the attributes ranked as the three most important in the initial ranking while the attributes ranked in the fifth and sixth positions were the most affected by discussion.

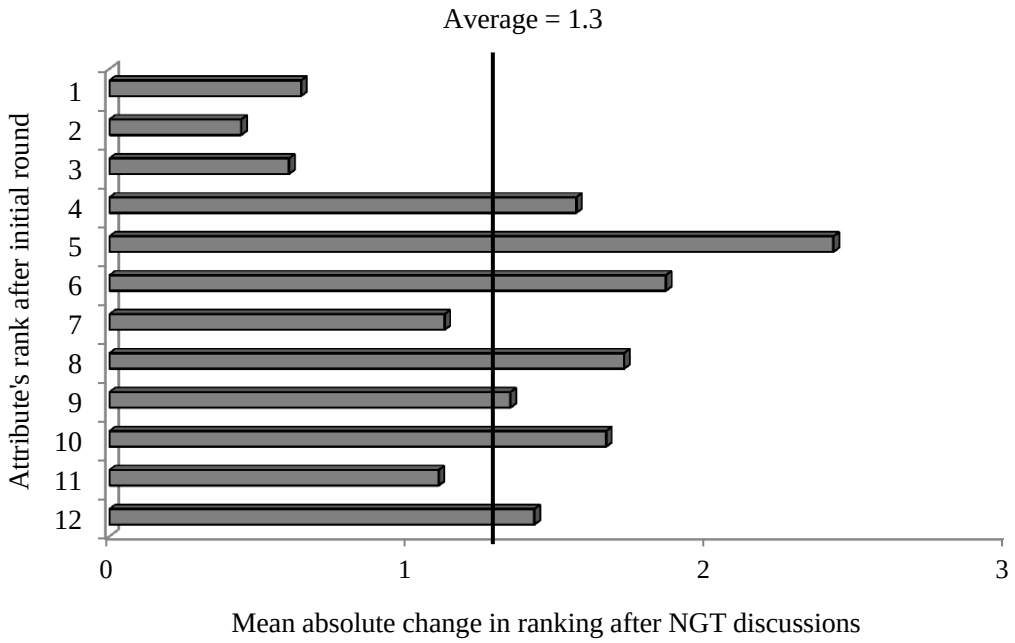
**Table 4|** *Different profiles of responders after NGT discussion* [a]

| | **Number of patients** | **Average absolute change between attributes' rankings: mean (standard deviation)** [b] | **Number of attributes changed: mean (standard deviation)** |
|---|---|---|---|
| Profile 1 *(0)* | 5 | 0 (0) | 0 (0) |
| Profile 2 *(>0-1)* | 6 | 0.85 (0.13) | 6.7 (1.4) |
| Profile 3 *(>1-2)* | 9 | 1.76 (0.13) | 8.5 (0.7) |
| Profile 4 *(>3)* | 5 | 2.58 (0.27) | 10.8 (1.4) |

[a] *Profiles of responders were determined based on the average absolute change between attributes' rankings. Profiles' classification is provided in parentheses in the first column.*

[b] *The average absolute change between attributes' rankings was obtained by summing, for each attribute, the absolute change between initial and final ranking (a positive change (+1) or a negative change (-1) are treated the same (+1)) and dividing by the number of attributes.*

**Figure 2|** *Mean absolute change in ranking of attributes after NGT discussion according to their rank in the initial round* [a]




[a] *This graph shows that the attributes in the first three positions (that differ according to individual patient's ranking) are the most stable after NGT discussions.*

*ADDITIONAL FINDINGS*

First, fifteen percent of patients (4/26) did not correctly rank from 1 to 12 since they assigned the same number to different attributes. Second, the order of presenting of attributes in the rank system and nominal group discussion seems to influence the ranking. When the attributes were presented in the first positions of the list, they generally obtained their highest score. Third, group analyses suggest that out-of-pocket was not in the top four in the two Dutch groups (5th and 11th position) reflecting that, in contrast with Belgian patients (ranked as 3rd, 5th and 8th), they have no out-of-pocket contribution for medications. No other major differences were observed between groups. Finally, only one patient included a missing attribute, i.e. drug interactions, which has been previously discussed.

*FINAL ATTRIBUTES SELECTION*

Rankings and NGT discussions revealed four important attributes that were consistently identified as important for patients: effectiveness, side effects, mode and frequency of administration. Interestingly, out-of-pocket cost was considered important in Belgium but not in the Netherlands reflecting that, in contrast with Belgian patients, they have no out-of-pocket contribution for medications. This result could suggest that out-of-pocket cost could only be included in countries (like Belgium) where it is relevant. Time on market was, for most patients, related to safety and lower side-effects which are already included as an attribute. Place of administration is highly

correlated with the mode of administration and will rather be incorporated in the description of the mode of administration. Other attributes were not sufficiently important for inclusion in the DCE based on ranking and discussions. Based on these considerations we decided to include the four first attributes for the DCE in the Netherlands and the fifth attribute (out-of-pocket cost) in Belgium only.

## DISCUSSION

We have demonstrated the feasibility of the NGT to prioritize attributes for inclusion in DCEs. When many candidate attributes are identified from available sources or patients interviews, this approach may be beneficial to assess the importance of these attributes to construct the DCE. In situations where the number of identified attributes need to be restricted, a two-stage analysis could therefore be performed, in which a self-exploratory analysis reduces the number of attributes (using NGT for example) and a DCE is conducted with the restricted list of attributes to further assess preferences for attributes' levels. Other tools (e.g. best-worst scaling, adaptive conjoint analysis where attributes are changed simultaneously) could be alternative approaches.

Starting from a comprehensive list of attributes for osteoporosis medication, generated from literature and expert opinion, we identified which osteoporosis medication attributes are important from the patients' perspective. Rankings and discussions revealed four important attributes: effectiveness, side effects, mode and frequency of administration.

These results are interesting for designing DCE experiments, but are also worthwhile by themselves when aiming at improving therapeutic adherence. Poor adherence to osteoporosis medications is a well-documented problem [20], and results in significant clinical and economic burden [21, 22]. Barriers to adherence include side-effects, inconvenient dosing regimens, lack of information and cost of medications [23]. Providing patients with adequate information on the treatment options and involving them in decision making may contribute to optimize treatment selection and to improve adherence to therapy [24, 25]. As drug therapies in osteoporosis differ according to side-effects, mode and frequency of administration and these were considered as important attributes in our research, sharing this information with the patients could lead to optimize treatment selection and to improve adherence to therapy.

In this study context, the NGT discussions did not substantially affect rank order of preferences for the attributes in the total group when compared to rank order before the NGT discussion, pointing to considerable agreement for the most important attributes. This could suggest that simple ranking exercise (or best-worst scaling) may perhaps be sufficient to determine the most important attributes. However, individual analyses have suggested that eighty percent of the patients changed their ranking after the discussion that could potentially reflect in a different group ranking. Further investigations in other contexts, other diseases or other decisional issues are therefore needed to

determine the added value of the NGT meeting when selecting and prioritizing attributes for a DCE or even other purposes.

The approach described here also has the advantage of being rigorous, systematic and transparent, and therefore to improve the face validity of DCEs. Many papers have pointed out that conjoint analysis did not justify very well the selection of attributes.[5, 19, 26] Recently, Coast et al. explored issues associated with attributes development for DCEs and contrasted different qualitative approaches in the development of DCEs based on experience generated in interviews [5]. Our study generated further insight by providing additional experience from group discussions. The benefits of conducting qualitative research were also not restricted to the selection of attributes. Discussions were interesting to refining language [5] and to conduct a Bayesian efficient design [27].The application of such method did, however, not come without a cost. We estimate that the whole process of organizing, running and analyzing the NGT cost about €10.000 (including about €1.500 as an incentive for the patients for the time spend and 2-3 months of a full-time researcher). We believe that the benefits of the approach make this however highly cost-effective.

The NGT could also be useful in selecting the initial set of attributes. Participants could first be asked to individually generate a list of important medication attributes, followed by a discussion phase to refining the list by adding, merging or removing attributes, and by the final individual ranking of the most important attributes. This was not done in our study since many potential attributes were already identified by the literature review and we also aimed to assess the impact of the NGT session on the rank order. Our patients had however the opportunity to add attributes to the list. Our study could also have some important implications for further research in this area. First, misunderstanding of attributes is frequent and a clear description and explanation of the attributes is required. Second, ranking many attributes could impose a substantial cognitive burden on respondents. Perhaps it would have been sufficient to ask patients to rank their five most important attributes. Rating scales per attribute could also be an alternative with much less effort on the respondent's part but with more limited information on the relative importance of attributes. Further work should be done to assess and compare ranking/rating exercises. Third, the impact of the NGT discussion was shown to substantially differ between patients. It would be interesting in the future to understand reasons that could explain this. Finally, our study showed that the attributes' presenting order did have an impact on the results. We therefore recommend controlling for ordering effects in ranking exercises.

A limitation of this study is that we have not compared the attributes derived from NGT with other approaches (e.g. experts' opinions, best-worst scaling). The gold standard would be the revealed preference but this outcome is also difficult to assess. Head to head comparisons of different techniques could help to assess and understand differences between approaches, although there may be practical limitations in developing such studies [5].

In conclusion, a nominal group technique is feasible for selecting attributes for DCE. Although, in this study context, the NGT discussions did not substantially affect the patients' rank order of preferences for the attributes when compared to rank order before the group discussion, this approach is rigorous, transparent and improves the face validity of future DCEs. Further work should be done to determine the added value of the NGT session, to assess the optimal ranking/rating method with control of ordering effects and to compare the attributes selected with different approaches.

## ACKNOWLEDGEMENTS

Financial support for this study was provided by Amgen. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing and publishing the report.

The authors thank Marian Curfs and Rita Deroisy for helping us to contact patients, and also all patients for their participation.

## REFERENCES


1. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health. 2011;14(4):403-13.
2. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics. 2008;26(8):661-77.
3. Ryan M, Bate A, Eastmond CJ, Ludbrook A. Use of discrete choice experiments to elicit preferences. Qual Health Care. 2001;10 Suppl 1:i55-60.
4. Ryan M, Gerard K, Amaya-Amaya M. Using discrete choice experiments to value health and health care. Dordrecht, the Netherlands. Springer. 2008.
5. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. Health Econ. 2012;21(6):730-41.
6. Louviere J, Flynn TN, Carson R. Discrete choice experiments are not conjoint analysis. Journal of Choice Modelling. 2010;3(3):57-72.
7. Rohrbaugh J. Improving the Quality of Group Judgment: Social Judgment Analysis and the Nominal Group Technique. Organ Behav Hum Perform. 1981;28:272-88.
8. Nominal group technique is reliable for deciding research priorities. BMJ. 2000;320(7240):E.
9. Vella K, Goldfrad C, Rowan K, Bion J, Black N. Use of consensus development to establish national research priorities in critical care. BMJ. 2000;320(7240):976-80.
10. Weiss TW, Gold DT, Silverman SL, McHorney CA. An evaluation of patient preferences for osteoporosis medication attributes: results from the PREFER-US study. Curr Med Res Opin. 2006;22(5):949-60.
11. Duarte JW, Bolge SC, Sen SS. An evaluation of patients' preferences for osteoporosis medications and their attributes: the PREFER-International study. Clin Ther. 2007;29(3):488-503.
12. Darba J, Restovic G, Kaskens L, Balbona MA, Carbonell A, Cavero P, et al. Patient preferences for osteoporosis in Spain: a discrete choice experiment. Osteoporos Int. 2011;22(6):1947-54.
13. de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Pols HA, Koes BW, Steyerberg EW. Patients' preferences for osteoporosis drug treatment: a discrete choice experiment. Osteoporos Int. 2008;19(7):1029-37.
14. Fraenkel L, Gulanski B, Wittink D. Patient treatment preferences for osteoporosis. Arthritis Rheum. 2006;55(5):729-35.
15. Lee S, Glendenning P, Inderjeeth CA. Efficacy, side effects and route of administration are more important than frequency of dosing of anti-osteoporosis treatments in determining patient adherence: a critical review of published articles from 1970 to 2009. Osteoporos Int. 2011;22(3):741-53.
16. Rizzoli R, Reginster JY, Boonen S, Breart G, Diez-Perez A, Felsenberg D, et al. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. Calcif Tissue Int. 2011;89(2):91-104.
17. Drennan V, Walters K, Lenihan P, Cohen S, Myerson S, Iliffe S. Priorities in identifying unmet need in older people attending general practice: a nominal group technique study. Fam Pract. 2007;24(5):454-60.

18. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ. 2012;21(2):145-72.
19. Marshall D, Bridges JF, Hauber B, Cameron R, Donnalley L, Fyie K, et al. Conjoint Analysis Applications in Health - How are Studies being Designed and Reported?: An Update on Current Practice in the Published Literature between 2005 and 2008. Patient. 2010;3(4):249-56.
20. Rabenda V, Hiligsmann M, Reginster JY. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. Expert Opin Pharmacother. 2009;10(14):2303-15.
21. Hiligsmann M, Rabenda V, Bruyere O, Reginster JY. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy. 2010;96(2):170-7.
22. Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. Value Health. 2012;15(5):604–612.
23. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-97.
24. Montori VM, Shah ND, Pencille LJ, Branda ME, Van Houten HK, Swiglo BA, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. Am J Med. 2011;124(6):549-56.
25. Elwyn G, Edwards A, Britten N. What information do patients need about medicines? "Doing prescribing": how doctors can be more effective. BMJ. 2003;327:864-7.
26. Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. BMJ. 2000;320(7248):1530-3.
27. Rose JM, Bliemer MCJ, Hensher DA, Collins AT. Designing efficient stated choice experiments in the presence of reference alternatives. Transport Res B-Meth. 2008;42(4):395-406.

# CHAPTER 9

## PATIENTS' PREFERENCES FOR OSTEOPOROSIS DRUG TREATMENT: A DISCRETE-CHOICE EXPERIMENT

**Hiligsmann M**, Dellaert B, Dirksen C, van der Weijden T, Reginster JY, Goemaere S, Watson V, Boonen A.

*Arthritis Research & Therapy 2014, 16(1), R36*

## ABSTRACT

*INTRODUCTION:* The patient's perspective is becoming increasingly important in clinical and policy decisions. In this study, we aimed to evaluate the preferences of patients with, or at risk of, osteoporosis for medication attributes, and to establish how patients trade between these attributes.

*MATERIALS AND METHODS:* A discrete choice experiment survey was designed and patients were asked to choose between two hypothetical unlabelled drug treatments (and an opt-out option) that vary in five attributes: efficacy in reducing the risk of fracture, type of potential common side-effects, mode and frequency of administration and out-of-pocket costs. An efficient experimental design was used to construct the treatment option choice sets and a mixed logit panel data model was used to estimate patients' preferences and trade-offs between attributes.

*RESULTS:* A total of 257 patients with, or at risk of, osteoporosis completed the experiment. As expected, patients preferred treatment with higher effectiveness and lower cost. They also preferred either an oral monthly tablet or 6-month subcutaneous injection above weekly oral tablets, 3-month subcutaneous, 3-month intravenous or yearly intravenous injections. Patients disliked being at risk of gastro-intestinal disorders more than being at risk of skin reactions and flu-like symptoms. There was significant variation in preferences across the sample for all attributes except subcutaneous injection.

*CONCLUSION:* This study revealed that osteoporotic patients preferred 6-month subcutaneous injection and oral monthly tablet, and disliked gastro-intestinal disorders. Moreover, patients were willing to pay a personal contribution or to trade treatment efficacy for better levels of other attributes. Preferences for treatment attributes varied across patients and this highlight the importance to clinical decision-making of understanding individual patients' preferences to improve osteoporosis care.



## KEY WORDS

Discrete-choice experiment, drug treatment, osteoporosis, patients, preferences.

## INTRODUCTION

The patient's perspective is becoming increasingly important in clinical and policy decisions. Information about what patients need and prefer, and how they value various aspects of a health intervention can be useful when designing and evaluating health care programs [1]. A better understanding of patients' preferences for treatment can help health professionals to improve disease management. When differences in efficacy or safety do not determine the choice of a specific treatment patient's, satisfaction with therapy is important [2]. Addressing patients' concerns with treatment and involving them in clinical decision-making may also improve adherence [1]. Patients increasingly want to be informed by their doctors, and to be active in clinical decision-making [3, 4]. In recent years, discrete choice experiments (DCEs) have been increasingly used to elicit patients' preferences for health care [5, 6]. DCEs can quantify the relative importance of the various attributes that characterize a treatment and allow the trade-offs that respondents make between these to be quantified [7].

The aim of this study was to evaluate osteoporotic patients' preferences for medication attributes using a DCE, and to establish how patients make trade-offs between these attributes. This study differs from previously published DCEs in osteoporosis in several ways [8-10], First, this study includes recently introduced routes and timing of administration (e.g. subcutaneous and intravenous) and the nature of potential side-effects. Given potential differences in preferences between administration schemes, information on patients' preferences for these new administration schemes would be extremely useful for health professionals and decision makers [11]. Second, this study expands the population studied to include men. Third, a rigorous qualitative research was performed to select medication attributes [12].

## MATERIALS AND METHODS

### *DISCRETE CHOICE EXPERIMENT*

A DCE describes an intervention by its attributes (e.g. effectiveness, side-effects, costs) and reports how patient's preference for an intervention are influenced by the type and levels of these attributes [7]. In the DCE, patients were asked to choose between two unlabelled drug treatments (A and B) and a 'no treatment' (opt-out) option. The alternative treatments varied in several attributes, and patients were asked to select the treatment they would prefer. Patients were asked to make a series of such hypothetical choices. This research followed published DCEs guidelines [1, 13] and used rigorous methods to select treatment attributes, to design the DCE and to conduct the statistical analysis.

*ATTRIBUTES AND LEVELS*

The identification and selection of the DCE attributes is fundamental to obtain valid results [14, 15]. We conducted a nominal group technique to select the DCE attributes [14]. Full details on this are provided elsewhere [12]. In brief, patients' group discussions (4-8 participants per group, $n_{total}$=26) were conducted to prioritize a list of potentially important attributes of osteoporosis drug treatment. This list was developed from a literature review and discussions with experts. A ranking exercise and group discussions revealed five attributes that were consistently identified as important for patients: effectiveness, side effects, mode and frequency of administration and out-of-pocket cost (Table 1) [12]. Levels were assigned to these attributes based on the current treatment using a literature review and discussion with experts (n=5). For the side-effects of treatment, we focused on the types of common side-effects [16].

**Table 1**| *Attributes and levels for osteoporosis drug treatment*

| | |
|---|---|
| Efficacy in reducing the risk of future fractures | 20% |
| | 30% |
| | 40% |
| | 50% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal disorders |
| | Flu-like symptoms |
| | Skin reactions |
| Mode of administration | Oral tablet |
| | Subcutaneous injection |
| | Intravenous injection |
| Frequency of administration | Weekly |
| | Monthly |
| | Every 3 months |
| | Every 6 months |
| | Yearly |
| Cost to you (per month) | €5 |
| | €15 |
| | €25 |
| | €40 |
| | €60 |

*EXPERIMENTAL DESIGN*

It is not feasible to present an individual with all possible treatment combinations from the attributes and levels in Table 1. Experimental design techniques were used to draw a sub-set of treatment profiles to present to respondents in the DCE [5]. Specifically, a Bayesian efficient experimental design was used to select the subset using the software Ngene (Version 1.1.1,

http://www.choice-metrics.com/) to select the sub-set. This experimental design maximizes the precision of estimated parameters (by maximising the D-efficiency – a summary measure of the variance covariance matrix) for a given number of choice questions [17]. In this study, fifteen choice sets were created. An example of a choice set is shown in Figure 1.

**Figure 1**| *Example of a choice set*

**Question 1**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 30% | 40% |
| Possible side effects (affecting 1 in 50 patients) | Flu-like symptoms | Skin reactions |
| Mode of administration | Subcutaneous | Intravenous |
| Frequency of administration | 3-month | Yearly |
| Cost to you | €15 (per month) | €25 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

The construction of an efficient experimental design depends on the patients' preferences, therefore we conducted a pilot DCE study (n=10). We used the pilot results to obtain preliminary information about patients' preferences and then used this information to create the experimental design for the main study. The pilot DCE experimental design used a-priori information about patients preferences based on literature review [9] and discussions during the qualitative research (e.g. higher effectiveness is preferred). We also wished to avoid presenting respondents with implausible treatment options (e.g. a yearly oral tablet), therefore we restricted the experimental design to include only realistic combinations between mode and frequency of administration that could appear in the design (i.e. oral weekly or monthly tablets, subcutaneous every 3 or 6 months, and intravenous every 3-month or yearly). The experimental design based on pilot preference information suggested that 200 respondents would be sufficient power to detect the significance of most parameters.

*QUESTIONNAIRE, DATA COLLECTION AND PATIENT RECRUITMENT*

In the questionnaire, patients received a thorough description of the DCE task. The attributes and levels were carefully explained and an example of a completed choice set was provided. One of the choice questions was asked twice to assess test-retest reliability. Each patient therefore received 16

choice sets. After completion of the choice tasks, respondents were asked how difficult they found the choice tasks on a seven-point scale. The DCE task is provided in Additional file 1. The questionnaire also asked questions on patients' characteristics. Individual 10-year probabilities of a hip and a major osteoporotic fracture (FRAX® score) were calculated for each respondent by a doctor/researcher and added to the questionnaire afterwards.

The questionnaire was developed in English by the working group that include a patient, clinical and DCE experts and was approved by two native English speakers, experts in osteoporosis. The questionnaire was then translated in French and Dutch by a medical translation company specialising in the translation of patient reported outcome measures (PharmaQuest Ltd) and the translation was checked and approved by two native French and Dutch speakers with medical backgrounds. The questionnaire was pilot tested with 15 patients (French-speaking = 10, Dutch-speaking = 5) to check interpretation problems and face validity; no wording problems arose and only minor changes to layout were made.

Consecutive patients with, or at risk of, osteoporosis to whom medication (or lifestyle changes) was at least proposed were recruited during outpatients' clinics in two Belgian osteoporosis centres (Ghent and Liège). Explanation of the task and an example choice task was provided by the doctor or a researcher. The questionnaire was mainly completed by the patient at home and returned in a postage-paid envelope. Very few patients completed the questionnaire at the clinic but without any assistance from the doctor/researcher. Approval for this study was obtained from the ethics committee of Maastricht University Medical Center who coordinated this project and participants gave informed written consent.

*STATISTICAL ANALYSES*

From the DCE, we observe the respondent's choice of one treatment from the three alternatives presented in each choice set. Responses are analysed based on random utility theory [18]. In this case, the utility that a patient *i* assigns to a treatment *j*, $V_{ij}$, is modelled as the sum of two parts: a systematic part based on the attributes included in the DCE and an error part $\varepsilon_{ijt}$. We specify $V_{ij}$ as:

$$V_{ij} = \beta_0 + (\beta_1+\eta_{1i})\,\mathrm{EFFICACY_j} + (\beta_2+\eta_{2i})\,\mathrm{COST_j}$$

$$+ (\beta_3+\eta_{3i})\,\mathrm{ORAL\_1M_j} + (\beta_4+\eta_{4i})\,\mathrm{SUB\_3M_j} + (\beta_5+\eta_{5i})\,\mathrm{SUB\_6M_j} + (\beta_6+\eta_{6i})\,\mathrm{INT\_3M_j}$$

$$+ (\beta_7+\eta_{7i})\,\mathrm{INT\_1Y_j} + (\beta_8+\eta_{8i})\,\mathrm{FLUSYMPT_j} + (\beta_9+\eta_{9i})\,\mathrm{SKINREACT_j} + \varepsilon_{ij}$$

$\beta_0$ is the constant reflecting the preferences for selecting treatment relative to no treatment, $\beta_1$-$\beta_9$ are the mean attribute utility weights in the population and $\eta_{1i}$-$\eta_{9i}$ are error terms capturing individual-specific unexplained variation in the utility weights. Dummy coding was used (for ease of interpretation of the results) to describe all categorical variables ($\beta_3$-$\beta_9$). Reference levels for mode of administration and for side effects are weekly oral tablet and risk of gastro-intestinal disorders,

respectively. The sign of the coefficient reflects whether the attribute/level has a positive or a negative effect on treatment utility compared to the base level. The value of a coefficient indicates the relative importance of the attribute/level.

When developing a statistical model of respondents' choice it is important to account for respondents completing up to 15 choice tasks each and to allow preferences for treatment to vary across the sample., therefore, a mixed logit panel data model was estimated using Nlogit, version 5 [19]. This model allows model parameters (preferences) to vary in the population. This is achieved by specifying a random parameter that has a distribution and estimating the mean (β) and standard deviation of the error term (η) to capture the parameter's distribution. If the standard deviation is significantly different from zero this is interpreted as evidence of significant preference variation for the attribute in the sample.

Initially, we estimated models in which preferences for all attributes could vary in the population and then in the final model, those attributes for which the estimated standard deviation was not significant (5% level), the preferences were specified to be the same in the population (fixed parameters). The random parameters for cost and efficacy were drawn from a log-normal distribution - this allows us to constrain the parameter estimate to be either negative (for cost) and positive (for efficacy) [19]. All other random parameters were drawn from a normal distribution. The estimation was conducted by using 2000 Halton draws.

We also calculated marginal willingness to pay (WTP) and marginal willingness to trade efficacy (WTTE) of the attributes/levels. This allows us to compare preferences for all attributes measured with a common and interpretable metric either money or efficacy. A WTP (or WTTE) value represents how much one is willing to pay (or to trade) for a one unit change in the attribute, and is calculating by taking the ratio of the mean parameter for the attribute/level to the mean parameter related to the cost (or efficacy). As the cost and efficacy variables were estimated as random parameters, the WTP and WTTE calculations must take this into account. As recommended in this case, the conditional constrained parameters were used [19].

The mixed logit model identifies attributes for which there is significant preference variation, but it does not explain why this variation exists. To understand the potential sources of preference variation, additional analyses included covariates (such as gender, age) in the model one by one. Significant covariates were then included together and non-significant covariates were excluded from this model. Adjusted pseudo R-squared and finite Akaike Information Criterion were used to enable comparison of models with and without covariates. We also tested whether patients using a specific mode of administration had a stronger preference for this administration scheme by incorporating interactions between levels and covariates. Furthermore, to explore the impact of respondents who failed the test-retest, a sensitivity analysis was conducted by excluding these individuals. A subgroup analysis was also conducted in patients with high-risk of fractures (defined

as a FRAX®-major risk >10%) and with low-risk of fractures. To assess the significance of the differences between populations, a joint model was estimated using interaction terms.

## RESULTS

### *PATIENTS' CHARACTERISTICS*

A total of 301 questionnaires were distributed to patients. Of these, 268 were returned representing a response rate of 89%. Eleven questionnaires were excluded because the patient did not complete at least five choice sets in DCE task. A total of 257 (85%) questionnaires were included for data analysis. Respondents' socio-demographics and health characteristics are shown in Table 2. There was no restriction on participation based on patients race and ethnicity but patients were mainly Caucasian.

**Table 2**| *Patients' characteristics*

| | |
|---|---|
| Age (years, mean ±SD) | 67.1±10.4 |
| Female gender | 83.3% |
| Educational level | |
| Primary | 8.4% |
| Some high school | 35.9% |
| High school graduate | 30.3% |
| College or University | 25.5% |
| Size of household | |
| 1 person | 29.9% |
| 2 people | 55.1% |
| 3 people+ | 15.0% |
| Monthly household income (€) | |
| Up to 999 | 5.5% |
| 1,000-1,499 | 33.1% |
| 1,500-1,999 | 19.1% |
| 2,000-2,499 | 17.8% |
| 2,500-2,999 | 11.9% |
| 3,000+ | 12.7% |
| Diagnosis of osteoporosis | 89.8% |
| Years since osteoporosis (mean ±SD) | 8.9±0.3 |
| With prior fracture(s) | 52.5% |
| In the last year | 22.8% |
| Patients on osteoporotic treatment | 69.8% |
| Administration mode of current treatment | |
| Oral | 72.2% |
| Subcutanous | 15.4% |
| Intravenous | 12.4% |
| Number of co-treatments | |
| 0-1 | 19.3% |
| 2-3 | 40.6% |
| 4+ | 40.2% |
| 10-year probability of a major osteoporotic fracture (FRAX) (mean ±SD) | 14.3% ± 7.5% |
| 10-year probability of a hip fracture (FRAX) (mean ±SD) | 6.1% ± 5.3% |

The difficulty of the task on a seven-point scale (1 for extremely easy and 7 for extremely difficult) was estimated on average between 3 and 4. The task was found to be extremely easy for 35 patients (13.6%) while 19 patients (7.4%) gave a score of 6 of 7. A total of 219 patients (85.2%) chose the same alternative in the test-retest exercise. This is in line with existing test-retest results [15].

*PATIENTS' PREFERENCES*

The distribution of choices across the choice sets is provided in Additional file 2. The main results of the mixed logit model are presented in Table 3. The estimated coefficients for efficacy and costs had the expected sign and were statistically significant. The positive sign of the efficacy parameter indicates that respondents prefer higher treatment efficacy and the negative sign of the cost parameter indicates that respondents prefer paying less money for treatment. Patients prefer a 6-month subcutaneous injection and a monthly oral tablet compared with a weekly oral tablet (base level). There were no significant differences between weekly oral tablet, 3-month subcutaneous and yearly intravenous; nor/neither between 6-month subcutaneous injection and monthly oral tablet. Regardless of administration mode, patients preferred a longer dosing regimen (monthly *vs* weekly oral tablet; 6-month *vs* 3-month subcutaneous; yearly *vs* 3-month intravenous). The positive sign for the two side-effects parameters indicates that patients disliked being at risk of gastro-intestinal disorders (base) more than being at risk of skin reactions or flu-like symptoms.

**Table 3**| *Results from the panel mixed logit model*

| Attributes and levels | Estimate (95% CI) | P Value | Standard deviation |
|---|---|---|---|
| Constant | 0.90*** (0.62 to 1.17) | 0.00 | --- |
| Efficacy (1% risk reduction) | 0.07*** (0.05 to 0.08)$ | 0.00 | 1.19*** (1.06 to 1.30) |
| Cost per month (€1) | -0.05*** (-0.04 to -0.06)$ | 0.00 | 1.24*** (1.09 to 1.39) |
| Drug administration (reference level: weekly oral tablet) | | | |
| Monthly oral tablet | 0.69*** (0.36 to 1.03) | 0.00 | 0.92*** (0.65 to 1.19) |
| Subcutaneous 3-month | 0.16 (-0.09 to 0.42) | 0.21 | NS† |
| Subcutaneous 6-month | 0.75*** (0.44 to 1.07) | 0.00 | NS |
| Intravenous 3-month | -0.57** (-1.12 to -0.01) | 0.05 | 2.62*** (2.04 to 3.20) |
| Intravenous yearly | 0.28 (-0.12 to 0.68) | 0.17 | 1.56*** (1.17 to 1.94) |
| Side effects (reference level: gastro-intestinal disorders) | | | |
| Flu-like symptoms | 0.97*** (0.76 to 1.18) | 0.00 | 0.90*** (0.65 to 1.15) |
| Skin reactions | 0.63*** (0.41 to 0.85) | 0.00 | 1.04*** (0.81 to 1.26) |

*Number of observations 3,822 (257 respondents X 15 choices, minus 33 missing values)*
*Pseudo R-squared = 0.42; Log-likelihood -2456.03; AIC = 1.29.*
** p<0.10, ** p<0.05, *** p<0.01; † NS Not significant and not included in the final model; $ For the coefficients of efficacy and cost to you, exp(β) is shown. The standard deviation of the log-normal distribution is reported.*

The standard deviation parameters were statistically significant for all attributes except the subcutaneous injection, suggesting the presence of preference variation in the importance of the attribute/level across respondents. To gain more insight into how preferences vary, the distributions of the parameters or kernel density estimates of the individual parameter are provided in Additional file 3 – Figure 1.

*WILLINGNESS TO PAY*

The WTP and WTTE for attributes/levels are presented in Table 4. For example, respondents were willing to pay a personal contribution of €19.53 more per month or to give up 13.52% of drug's efficacy for the treatment mode 6-month subcutaneous injection rather than a weekly oral tablet.

**Table 4**| *Willingness to pay and willingness to trade efficacy for osteoporosis medication attributes**

| Attributes and levels | Willingness to pay (€ per month) Mean (95% CI) | Willingness to trade efficacy (% risk reduction) Mean (95% CI) |
|---|---|---|
| Efficacy (1% risk reduction) | 3.73 (3.01 to 4.44) | --- |
| Cost (€1) | --- | -2.27 (-1.58 to -2.96) |
| Drug administration (reference level: weekly oral tablet) | | |
| Monthly oral tablet | 16.16 (12.85 to 19.47) | -10.16 (-7.88 to -12.50) |
| Subcutaneous 3-month | 4.24 (3.72 to 4.76) | -2.93 (-2.57 to -3.30) |
| Subcutaneous 6-month | 19.53 (17.15 to 21.92) | -13.52 (-11.82 to -15.22) |
| Intravenous 3-month | -15.28 (-23.23 to -7.34) | 8.66 (14.31 to 3.01) |
| Intravenous yearly | 11.75 (5.64 to 17.85) | -5.83 (-1.88 to -9.77) |
| Side effects (reference level: gastro-intestinal disorders) | | |
| Flu-like symptoms | 25.21 (13.06 to 20.50) | -16.68 (-14.20 to -19.16) |
| Skin reactions | 16.78 (13.06 to 20.50) | -9.48 (-7.13 to -11.83) |

** Using the conditional constrained distribution*

*A positive willingness to pay means that patients are willing to pay a personal contribution for the attribute/level, while a negative willingness to trade efficacy means that patients are willing to give up treatment efficacy for the attribute/level.*

*HIGH VERSUS LOW-RISK PATIENTS*

The results of the model for high-risk and low-risk patients are presented in Table 5. Significant differences in preferences were found between these patients groups for the effectiveness and cost of treatment – the interactions between risk group and effectiveness and cost parameters were significant (5% level)). Lower effectiveness and higher costs are more acceptable for patients with high-risk of fractures. In addition, high-risk patients attached a higher (negative) value to being at risk for skin reactions than low-risk patients, and the constant (i.e. preferences for drug treatment per se) was higher for high-risk patients. Preferences for drug administration did not differ significantly between patients groups.

**Table 5|** *Differences between high and low-risk patients' preferences for osteoporosis drug treatment*

| Attributes and levels | High risk patients (FRAX-major >10%) Estimate (95% CI) SD | Low-risk patients (FRAX-major ≤10%) Estimate (95% CI) SD | P Value † |
|---|---|---|---|
| Number of patients | 139 | 114 | |
| Pseudo R-squared | 0.39 | 0.42 | |
| Log-likelihood | -1378.35 | -1085.55 | |
| Constant | 1.50*** (1.17 to 1.83) | -0.05 (-0.52 to 0.43) | 0.01 |
| Efficacy (1% risk reduction) | 0.04*** (0.03 to 0.04) SD: 1.65*** | 0.14*** (0.11 to 0.17) SD: 1.01*** | 0.00 |
| Cost per month (€1) | -0.02*** (-0.02 to -0.03) SD: 1.45*** | -0.08*** (-0.06 to -0.09) SD: 0.67*** | 0.00 |
| Drug administration (reference level: weekly oral tablet) | | | |
| Monthly oral tablet | 0.57** (0.08 to 1.06) SD: 0.94*** | 1.14*** (0.47 to 1.82) SD: 1.87*** | 0.14 |
| Subcutaneous 3-month | 0.14 (-0.19 to 0.47) SD: NS | 0.28 (-0.17 to 0.74) SD: NS | 0.14 |
| Subcutaneous 6-month | 0.57*** (0.17 to 0.96) SD: NS | 1.55*** (0.97 to 2.14) SD: NS | 0.06 |
| Intravenous 3-month | -0.28 (-0.88 to 0.31) SD: 1.82*** | -0.24 (-1.39 to 0.91) SD: 4.84*** | 0.25 |
| Intravenous yearly | 0.28 (-0.13 to 0.69) SD: 0.81*** | 0.75** (0.05 to 1.45) SD: 2.15*** | 0.33 |
| Side effects (reference level: gastro-intestinal disorders) | | | |
| Flu-like symptoms | 0.66*** (0.36 to 0.95) SD: 0.91*** | 1.51*** (1.07 to 1.95) SD: 1.18*** | 0.57 |
| Skin reactions | 0.45** (0.05 to 0.85) SD: 1.31*** | 0.49** (0.10 to 0.87) SD: 1.04*** | 0.05 |

** p<0.10, ** p<0.05, *** p<0.01; SD Standard deviation; NS not significant; † p Value was estimated in a joint model with interaction terms.*

*ADDITIONAL ANALYSES*

Excluding respondents who failed the test-retest (n=38) had no impact on the relative importance of the attributes (Additional file 3 – Model 1). The inclusion of more covariates into the model did not significantly improve the adjusted McFadden's pseudo-$R^2$ but reduced the sample size by 17% due to missing values (Additional file 3 – Model 2). Therefore we did not include these covariates in the reference model. The only significant covariate effects we observed were that the preference for drug treatment was higher for men and patients with higher income (monthly household income >€2,500 per month). Other parameters were not affected by the inclusion of covariates. In addition, patients did not significantly prefer their current mode of administration over another mode of administration.

## DISCUSSION

This study suggests that patients with, or at risk of, osteoporosis have preferences for medications' attributes and are willing to trade between attributes when making treatment choices. Our results are consistent with a priori expectations that patients prefer higher efficacy, lower costs and less frequent dosing regimens. In addition, patients preferred 6-month subcutaneous injection or monthly oral tablet over weekly oral tablet or intravenous injections, and they disliked being at risk for gastro-intestinal disorders. Patients are willing to trade efficacy or to pay a personal contribution for better levels of other attributes. For most of the attributes, there was significant variation in patients' preferences.

Previous DCEs have investigated women's preference for osteoporosis drug treatment [8-10]. Our results confirm the findings of de Bekker-Grob et al. [9] that patients prefer monthly oral tablet to weekly oral tablet and those of Darba et al. [8] suggesting no significant difference in preference between weekly oral regimen and yearly intravenous. Fraenkel et al. [10] also showed that preferences are strongly influenced by route of administration but suggest that a majority (65%) of Americans preferred yearly intravenous infusion over weekly oral tablet. Our study expands on the insights of these studies. We expand the population studied to include men, new recent administration routes and frequencies (e.g. 6-month subcutaneous injection) and the nature of potential side-effects. A rigorous qualitative research was also conducted to select attributes.

Results of this study could be very useful for health professionals and decision makers, especially given the poor adherence to weekly oral regimens and the potential differences in healthcare costs associated with osteoporosis medications. Non-adherence to medication is a major problem among patients with osteoporosis and affects considerably the effectiveness and cost-effectiveness of drug therapy [20, 21]. Determinants of poor adherence include inconvenient regimens [22]. In our study, many patients preferred a 6-month subcutaneous injection compared to weekly oral tablets and yearly intravenous injections. The recent introduction of 6-month subcutaneous injection of denosumab [23] and the recognition of the importance of patients' preferences could therefore potentially improve patient satisfaction and adherence with therapy [24]. Our results could also inform health-care decision making, in particular for drug reimbursement, where insights into the preferences of patients groups should be taken into account alongside medical and economic considerations [25].

In addition, the variation in the patients' preferences for attribute's levels observed in our study highlights the importance to take into account individual preferences into clinical decision-making to improve osteoporosis care. Relying solely on sample average preferences will probably be insufficient to optimise medical doctors' sensitivity to the preferences of individual and unique patient during a consultation. Informing individual patients about alternative options and their

outcomes, and involving them in decision making, would be very important to improve patient's satisfaction and the outcome of medical care [26].

Our study has some potential limitations. First, although consecutive patients were invited to participate in this study, we cannot exclude selection bias as some patients did not want, or were not able, to fill in the questionnaire. Second, generalizability and transferability of our findings may be limited recruiting patients in two osteoporosis centres in one country only. A cross-country comparison is on-going in seven European countries. Preferences for attributes/levels may differ according to a number of factors including age, income, education or prior fractures [27]. While we do not find evidence of preference variation associated with these factors in our study, the cross country comparison will investigate this further. Third, we focussed on the nature of common side-effects and not on their frequency and rare complications. Rare adverse events will be as (in)frequent in all categories of anti-resorptive drugs. So, adding osteonecrosis of the jaw and atypical femoral fracture to the side effect attribute would probably not differentiate between patient preferences across existing drugs. Attributes were selected using a rigorous qualitative method as recommended in good practice guidelines [1, 13]. Finally, it could be pointed out that the individual 10-year probability of fractures was not provided to the patients before completing the questionnaire. Only 35 (14%) patients reported knowing their FRAX® score.

## CONCLUSIONS

In conclusion, this study revealed that osteoporotic patients prefer 6-month subcutaneous injection and oral monthly tablets, and disliked gastro-intestinal disorders. Moreover, they were willing to trade efficacy or to pay a personal contribution for their preferred outcomes. We found differences in preferences across patients which highlights the importance of clinical decision-making taking individual preferences into account to improve osteoporosis care.

## AUTHORS' CONTRIBUTIONS

Design of the study: MH, AB, BD, CD, TVW, VW. Data collection: SG, JYR. Data analysis: MH, AB, BD, CD, VW. MH had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. MH drafted the manuscript and all others authors revised it critically for important intellectual content. All authors approved the final version.

## ACKNOWLEDGEMENTS

Financial support for this study was provided by Amgen. The funding agreement ensured the authors' independence in designing the study, interpreting the data, and writing and publishing the report. An ESCEO-Amgen Osteoporosis Fellowship grant received at the World Congress on Osteoporosis (IOF WCO-ECCEO10, Florence 2010) was also used to collect data in Belgium.

The authors would like to thank Jolien Delahaye, Jean-Marc Kaufman, Joke Poppe, Véronique van den Bossche (Ghent University Hospital), Rita Deroisy, Sandra Lambrechts, Lorenzo Leonori (University of Liege) for helping us in data collection; Ed Porquie, our patient partner; Wafa Ben Sedrine for data entry; John Rose for help in experimental design and all the patients for their participation. Finally, we also thank two reviewers for critical review and helpful comments on the manuscript.

## REFERENCES


1. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health. 2011;14(4):403-13.
2. Brennan PF, Strombom I. Improving health care by understanding patient preferences: the role of computer technology. J Am Med Inform Assoc. 1998;5(3):257-62.
3. Salzburg Global Seminar. Salzburg statement on shared decision making. BMJ. 2011;342:d1745.
4. Fleurence RL, Iglesias CP, Torgerson DJ. Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. Osteoporos Int. 2006;17(1):29-40.
5. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ. 2012;21(2):145-72.
6. Marshall D, Bridges JF, Hauber B, Cameron R, Donnalley L, Fyie K, et al. Conjoint Analysis Applications in Health - How are Studies being Designed and Reported?: An Update on Current Practice in the Published Literature between 2005 and 2008. Patient. 2010;3(4):249-56.
7. Ryan M. Discrete choice experiments in health care. BMJ. 2004;328(7436):360-1.
8. Darba J, Restovic G, Kaskens L, Balbona MA, Carbonell A, Cavero P, et al. Patient preferences for osteoporosis in Spain: a discrete choice experiment. Osteoporos Int. 2011;22(6):1947-54.
9. de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Pols HA, Koes BW, Steyerberg EW. Patients' preferences for osteoporosis drug treatment: a discrete choice experiment. Osteoporos Int. 2008;19(7):1029-37.
10. Fraenkel L, Gulanski B, Wittink D. Patient treatment preferences for osteoporosis. Arthritis Rheum. 2006;55(5):729-35.
11. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int. 2007;18(8):1023-31.
12. Hiligsmann M, van Durme C, Geusens P, Dellaert BG, Dirksen CD, van der Weijden T, et al. Nominal group technique to select attributes for discrete choice experiments: an example for drug treatment choice in osteoporosis. Patient Pref Adherence. 2013;7:133-9.
13. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics. 2008;26(8):661-77.
14. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. Health Econ. 2012;21(6):730-41.
15. Ryan M, Gerard K, Amaya-Amaya M, editors. Using discrete choice experiments to value health and health care. Dordrecht: Springer. 2008.
16. Rizzoli R, Reginster JY, Boonen S, Breart G, Diez-Perez A, Felsenberg D, et al. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. Calcif Tissue Int. 2011;89(2):91-104.
17. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Muhlbacher A, Regier DA, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health 2013;16(1):3-13.
18. McFadden, D. The choice theory approach to market research. Marketing Science, 1986;5:275-279.

19. Hensher D, Rose J, Greene W. Applied choice analysis: a primer. Cambridge, UK. Cambridge University Press. 2007.
20. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med. 2009;122(2 Suppl):S3-13.
21. Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. Value Health. 2012;15(5):604-12.
22. Rossini M, Bianchi G, Di Munno O, Giannini S, Minisola S, Sinigaglia L, et al. Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int. 2006;17(6):914-21.
23. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.
24. Mulley AG, Trimble C, Elwyn G. Stop the silent misdiagnosis: patients' preferences matter. BMJ. 2012;345:e6572.
25. Hiligsmann M, Kanis JA, Compston J, Cooper C, Flamion B, Bergmann P, et al. Health technology assessment in osteoporosis. Calcif Tissue Int. 2013;93(1):1-14.
26. Montori VM, Shah ND, Pencille LJ, Branda ME, Van Houten HK, Swiglo BA, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. Am J Med. 2011;124(6):549-56.
27. Silverman S, Calderon A, Kaw K, Childers TB, Stafford BA, Brynildsen W, et al. Patient weighting of osteoporosis medication attributes across racial and ethnic groups: a study of osteoporosis medication preferences using conjoint analysis. Osteoporos Int. 2013;24(7):2067-77

**SUPPLEMENT FILE 1: QUESTIONNAIRE**

***Task: Making choices for drug therapy***

In this task, we are interested in your opinion on drug therapy for osteoporosis. In order to identify your opinion, we would like to ask you to make a series of choices between different drug therapies.

To help you make these choices, please read carefully through the following information.

**The task**

Please imagine that this is your first visit to a rheumatology clinic. You have recently been diagnosed with osteoporosis and your doctor has advised you that you should start taking medication.

In each of the following 16 choices, you will be offered two drug therapies (**A** or **B**). In each choice please state whether you would choose to take drug therapy A, drug therapy B, or **no treatment**. If you choose no treatment you would not receive treatment for your osteoporosis (and please assume that there are no other available treatment options).

The drug therapies you will be offered will differ in five ways: (1) their effect in reducing the risk of fractures, (2) side-effects, (3) mode of administration, (4) frequency of administration and (5) out-of-pocket costs. These 5 characteristics of the drug therapies will now be explained.

- **Efficacy (their effect) in reducing the risk of relevant fractures (**such as fractures of hip, wrist, shoulder or vertebrae) – this may be ***20%, 30%, 40%*** or ***50%***.

  Percentages can be a little difficult to understand in this context; so to help explain please refer to the following example:
  Based on individual risk factors (such as age, sex, weight, family history of fractures, previous fractures), assume that a person's risk for having a fracture in the next 10 years is 20%. Assume this value represents the average risk of fractures in elderly osteoporotic women.
  In that case, it would mean that:
  - Without any treatment, 20 women out of 100 will sustain a fracture within the next 10 years (20%)
  - With a treatment efficacy of 50%, 10 out of 100 women will sustain a fracture
  - With a treatment efficacy of 40%, 12 out of 100 women will sustain a fracture
  - With a treatment efficacy of 30%, 14 out of 100 women will sustain a fracture
  - With a treatment efficacy of 20%, 16 out of 100 women will sustain a fracture

- **Side-effects** – these may be ***gastro-intestinal disorders*** (such as nausea, diarrhea, constipation, vomiting, and loss of appetite), ***skin reactions*** (such as mild redness possibly itching followed by some roughness and feeling of tightness) and ***flu-like symptoms*** (low grade fever, mild muscle and headache).
  Assume **only one in every 50** patients treated will have a side effect. Each of these side-effects is relatively mild, disappears after a few days and has no long-term or severe consequences.

It is important to remember that the frequency of the occurrence of any side effects during the treatment is NOT dependent on the frequency of the administration of the drug.

- **Mode of administration** – this may be ***oral tablet, subcutaneous, intravenous***
  - ***Oral tablet***: This would be taken in the morning, at least 30 minutes before breakfast and it is important not to lie down for at least an hour after taking the tablet
  - ***Subcutaneous (injection under the skin)***: injection under your skin given to you by a doctor or nurse (at home or at the physician's office)
  - ***Intravenous (injection into the vein)***: given by infusion into your vein in a clinic or hospital setting. The infusion usually takes approximately 15 minutes

- **Frequency of administration** – this may be ***weekly, monthly, once every 3 months, once every 6 months*** or ***annually***

- **Personal contribution (cost to you) per month** – This may be ***€5, €15, €25, €40*** *or* ***€60***. If you are currently a medical card holder and therefore not paying for your drugs, for the purpose of this questionnaire can you please imagine that you should pay this amount yourself every month

**Example of the task** (please do not fill in)

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy in reducing the risk of future fractures | 30% | 20% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal side effects | Flu-like symptoms |
| Mode of administration | Intravenous | Oral tablet |
| Frequency of administration | Once yearly | Once weekly |
| Cost to you | €40 (per month) | €25 (per month) |

| Which treatment would you choose? | Treatment A | Treatment B | No treatment |
|---|---|---|---|
| *(Tick one box only)* | ☐ | X | ☐ |

In this example, you are asked to choose between **treatment A** which reduces your risk of future fractures by 30%, has some gastro-intestinal side-effects in one in 50 patients, is administered once per year by an intravenous infusion (into a vein) and has an out-of-pocket cost to you of €40 per month; **Treatment B** which reduces your risk of future fracture by 20%, can give mild flu-like symptoms to 1 in 50 patients, is taken as an oral tablet once weekly and the costs to you would be €25 per month; and **no treatment**. In the example above, the patient chooses treatment B, and therefore ticks the box treatment B.

Please choose from each of the following 16 choice sets your treatment of choice for the management of osteoporosis.

**Question 1**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 30% | 40% |
| Possible side effects (affecting 1 in 50 patients) | Flu-like symptoms | Skin reactions |
| Mode of administration | Subcutaneous | Intravenous |
| Frequency of administration | 3-month | Yearly |
| Cost to you | €15 (per month) | €25 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 2**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 20% | 50% |
| Possible side effects (affecting 1 in 50 patients) | Flu-like symptoms | Skin reactions |
| Mode of administration | Intravenous | Oral tablet |
| Frequency of administration | Yearly | Weekly |
| Cost to you | €60 (per month) | €5 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 3**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 20% | 40% |
| Possible side effects (affecting 1 in 50 patients) | Skin reactions | Flu-like symptoms |
| Mode of administration | Subcutaneous | Intravenous |
| Frequency of administration | 3-month | 3-month |
| Cost to you | €5 (per month) | €60 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 4**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 50% | 30% |
| Possible side effects (affecting 1 in 50 patients) | Skin reactions | Flu-like symptoms |
| Mode of administration | Subcutaneous | Oral tablet |
| Frequency of administration | 6-month | Monthly |
| Cost to you | €25 (per month) | €25 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 5**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 40% | 30% |
| Possible side effects (affecting 1 in 50 patients) | Skin reactions | Gastro-intestinal disorders |
| Mode of administration | Subcutaneous | Subcutaneous |
| Frequency of administration | 6-month | 3-month |
| Cost to you | €60 (per month) | €5 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 6**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 30% | 20% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal disorders | Flu-like symptoms |
| Mode of administration | Oral tablet | Oral tablet |
| Frequency of administration | Weekly | Monthly |
| Cost to you | €60 (per month) | €15 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 7**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 30% | 40% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal disorders | Skin reactions |
| Mode of administration | Oral tablet | Subcutaneous |
| Frequency of administration | Weekly | 3-month |
| Cost to you | €5 (per month) | €60 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 8**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 50% | 20% |
| Possible side effects (affecting 1 in 50 patients) | Skin reactions | Gastro-intestinal disorders |
| Mode of administration | Subcutaneous | Subcutaneous |
| Frequency of administration | 3-month | 6-month |
| Cost to you | €40 (per month) | €5 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 9**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 40% | 30% |
| Possible side effects (affecting 1 in 50 patients) | Flu-like symptoms | Gastro-intestinal disorders |
| Mode of administration | Intravenous | Subcutaneous |
| Frequency of administration | 3-month | 6-month |
| Cost to you | €15 (per month) | €40 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 10**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 30% | 40% |
| Possible side effects (affecting 1 in 50 patients) | Skin reactions | Gastro-intestinal disorders |
| Mode of administration | Oral tablet | Subcutaneous |
| Frequency of administration | Monthly | 3-month |
| Cost to you | €5 (per month) | €60 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 11**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 50% | 20% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal disorders | Skin reactions |
| Mode of administration | Oral tablet | Intravenous |
| Frequency of administration | Monthly | Yearly |
| Cost to you | €40 (per month) | €15 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 12**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 20% | 50% |
| Possible side effects (affecting 1 in 50 patients) | Flu-like symptoms | Gastro-intestinal disorders |
| Mode of administration | Subcutaneous | Oral tablet |
| Frequency of administration | 6-month | Monthly |
| Cost to you | €15 (per month) | €40 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 13**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 40% | 20% |
| Possible side effects (affecting 1 in 50 patients) | Flu-like symptoms | Skin reactions |
| Mode of administration | Intravenous | Intravenous |
| Frequency of administration | Yearly | 3-month |
| Cost to you | €40 (per month) | €25 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 14**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 20% | 50% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal disorders | Flu-like symptoms |
| Mode of administration | Intravenous | Subcutaneous |
| Frequency of administration | 3-month | 6-month |
| Cost to you | €25 (per month) | €40 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 15**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 40% | 30% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal disorders | Flu-like symptoms |
| Mode of administration | Oral tablet | Oral tablet |
| Frequency of administration | Monthly | Weekly |
| Cost to you | €25 (per month) | €15 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

**Question 16**

| | **Treatment A** | **Treatment B** |
|---|---|---|
| Efficacy (their effect) in reducing the risk of future fractures | 50% | 20% |
| Possible side effects (affecting 1 in 50 patients) | Skin reactions | Gastro-intestinal disorders |
| Mode of administration | Subcutaneous | Subcutaneous |
| Frequency of administration | 3-month | 6-month |
| Cost to you | €40 (per month) | €5 (per month) |

Which treatment would you choose? Treatment A ☐ Treatment B ☐ No treatment ☐

*(Tick one box only)*

Could you please state, on the following scale of 1 to 7, how easy or difficult this first task has been for you (i.e. the 16 choice questions). *(Circle one number only)*

| Extremely easy | | | | | | Extremely difficult |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |

## SUPPLEMENT FILE 2 - DISTRIBUTION OF CHOICES ACROSS THE CHOICE SETS

| | Treatment A | Treatment B | No treatment | Missing |
|---|---|---|---|---|
| Question 1 | 108 | 126 | 19 | 4 |
| Question 2 | 25 | 215 | 15 | 2 |
| Question 3 | 148 | 78 | 30 | 1 |
| Question 4 | 179 | 63 | 14 | 1 |
| Question 5 | 138 | 90 | 29 | 0 |
| Question 6 | 37 | 194 | 26 | 0 |
| Question 7 | 147 | 82 | 26 | 2 |
| Question 8 | 139 | 88 | 28 | 2 |
| Question 9 | 164 | 60 | 30 | 3 |
| Question 10 | 186 | 46 | 23 | 2 |
| Question 11 | 139 | 83 | 32 | 3 |
| Question 12 | 112 | 119 | 23 | 3 |
| Question 13 | 144 | 60 | 48 | 5 |
| Question 14 | 47 | 177 | 30 | 3 |
| Question 15 | 125 | 111 | 19 | 2 |

## SUPPLEMENT FILE 3 - ADDITIONAL RESULTS

**Model 1**| *Panel mixed logit model including only patients who were reliable in the test-retest exercise*

| Attributes and levels | Estimate (95% CI) | P Value | Standard deviation |
|---|---|---|---|
| Constant | 1.02*** (0.74 to 1.31) | 0.00 | --- |
| Efficacy (1% risk reduction) | 0.05*** (0.04 to 0.07) | 0.00 | 1.20*** (1.00 to 1.39) |
| Cost per month (€1) | -0.04*** (-0.04 to -0.05) | 0.00 | 1.16*** (1.02 to 1.31) |
| Drug administration (reference level: weekly oral tablet) | | | |
| Monthly oral tablet | 0.58** (0.22 to 0.95) | 0.00 | 0.95*** (0.67 to 1.22) |
| Subcutaneous 3-month | 0.11 (-0.16 to 0.38) | 0.44 | NS |
| Subcutaneous 6-month | 0.63*** (0.29 to 0.98) | 0.00 | NS |
| Intravenous 3-month | -0.45 (-1.07 to 0.17) | 0.15 | 2.60*** (1.94 to 3.26) |
| Intravenous yearly | 0.09 (-0.36 to 0.53) | 0.70 | 1.58*** (1.13 to 2.03) |
| Side effects (reference level: gastro-intestinal disorders) | | | |
| Flu-like symptoms | 0.94*** (0.70 to 1.17) | 0.00 | 0.90** (0.64 to 1.17) |
| Skin reactions | 0.61*** (0.37 to 0.85) | 0.00 | 1.00** (0.76 to 1.23) |

*Number of observations 3252 (219 X 15 choices, minus 33 missing values)*
*Pseudo R-squared = 0.41; Log-likelihood = -2092.78; AIC = 1.298.*
** p<0.10, ** p<0.05, *** p<0.01; NS Not significant*

**Model 2**| Panel mixed logit model including covariates

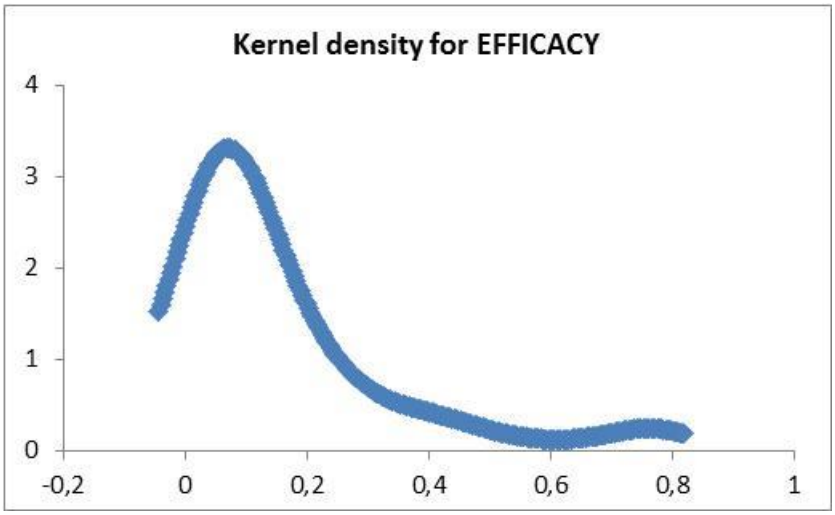
| Attributes and levels | Estimate (95% CI) | P Value | Standard deviation |
|---|---|---|---|
| Constant | 0.77*** (0.45 to 1.09) | 0.00 | --- |
| Efficacy (1% risk reduction) | 0.05*** (0.05 to 0.06) | 0.00 | 1.23*** (1.13 to 1.33) |
| Cost per month (€1) | 0.05*** (0.04 to 0.06) | 0.00 | 1.17*** (1.03 to 1.31) |
| Men | 0.84*** (0.48 to 1.20) | 0.00 | --- |
| High income | 0.28* (-0.04 to 0.59) | 0.09 | --- |
| Drug administration (reference level: weekly oral tablet) | | | |
| Monthly oral tablet | 0.67*** (0.28 to 1.06) | 0.00 | 1.03*** (0.69 to 1.36) |
| Subcutaneous 3-month | 0.06 (-0.24 to 0.35) | 0.55 | NS |
| Subcutaneous 6-month | 0.65*** (0.31 to 1.00) | 0.00 | NS |
| Intravenous 3-month | -0.66** (-1.27 to -0.04) | 0.04 | 2.96*** (2.25 to 3.68) |
| Intravenous yearly | 0.17 (-0.30 to 0.64) | 0.48 | 1.79*** (1.30 to 2.27) |
| Side effects (reference level: gastro-intestinal disorders) | | | |
| Flu-like symptoms | 1.12*** (0.86 to 1.37) | 0.00 | 0.99*** (0.70 to 1.27) |
| Skin reactions | 0.57*** (0.34 to 0.81) | 0.00 | 0.99*** (0.72 to 1.26) |

*Number of observations = 3215 (216 respondents X 15 choices, minus 25 missing values)*
*Pseudo R-squared = 0.42; Log-likelihood = -2062.73; AIC =1.29*
** p<0.10, ** p<0.05, *** p<0.01; † NS Not significant*
*Other covariates including age, education level, prior fractures, diagnosis of osteoporosis, size of household, being on treatment and number of co-treatments were not significant.*

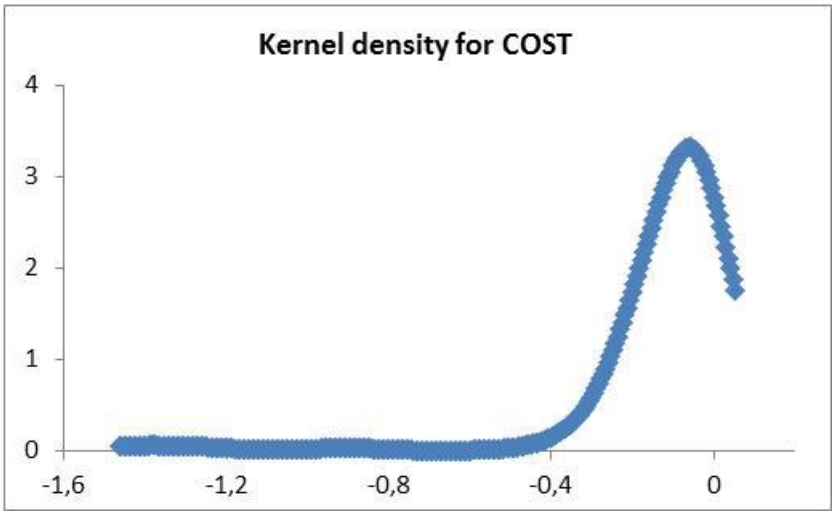
**Figure 1**| *Kernel density for the random parameters*

The kernel densities provide a visual representation of the possible variation in preferences for each of the attributes. The graphs indicate that there is significant variation in preferences for all attributes. For the mode of administration attribute levels, there is preference variation across each of the modes. However, the variation differs by mode. While there is preference variation for a monthly oral tablet compared with a weekly oral tablet, the majority of respondents prefer a monthly oral tablet as indicated by the majority of the distribution of the preferences being positive. However, for intravenous three monthly intravenous injection, the distribution of the preferences is both positive and negative indicating that while some patients significantly preferred this mode others did not.

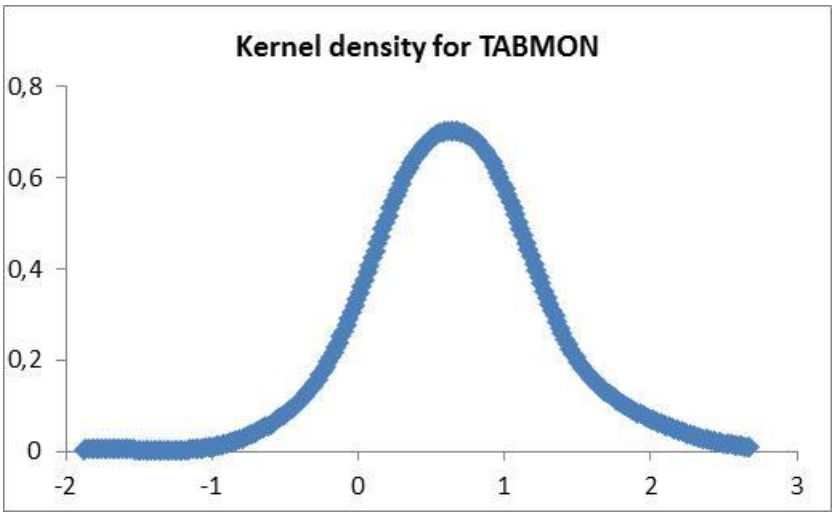
A. Efficacy



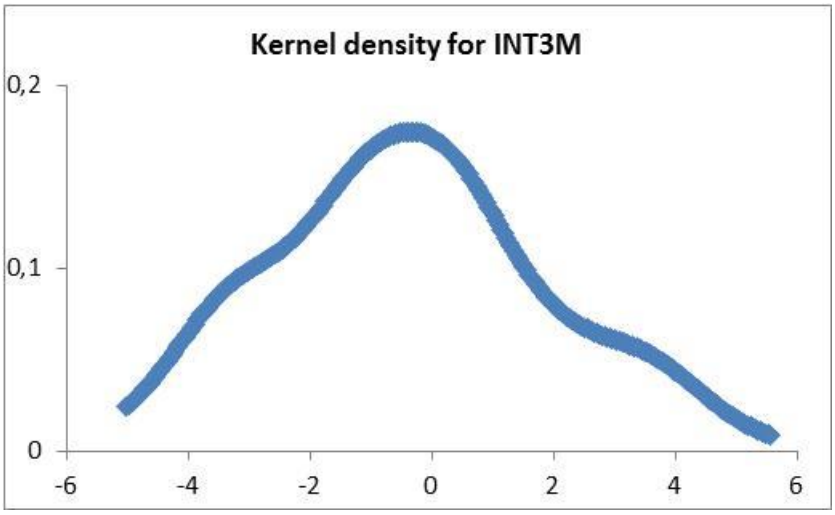

B. Cost



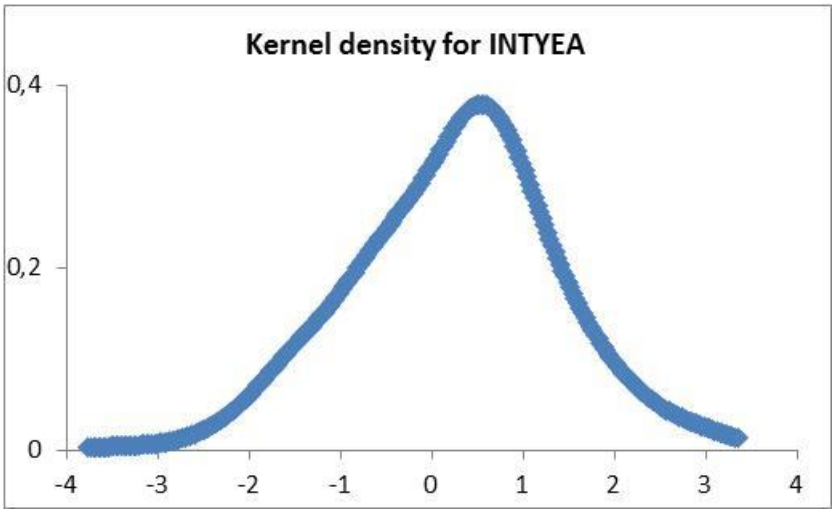

C. Oral monthly tablet



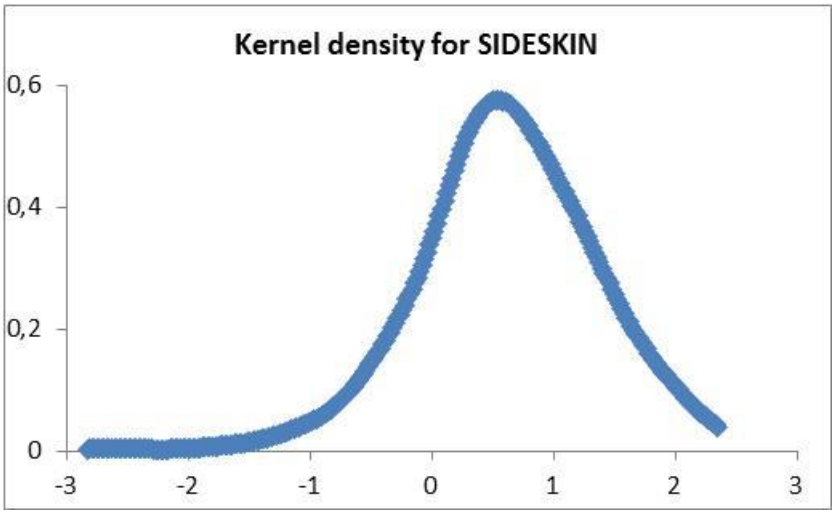
D. Intravenous every 3 months



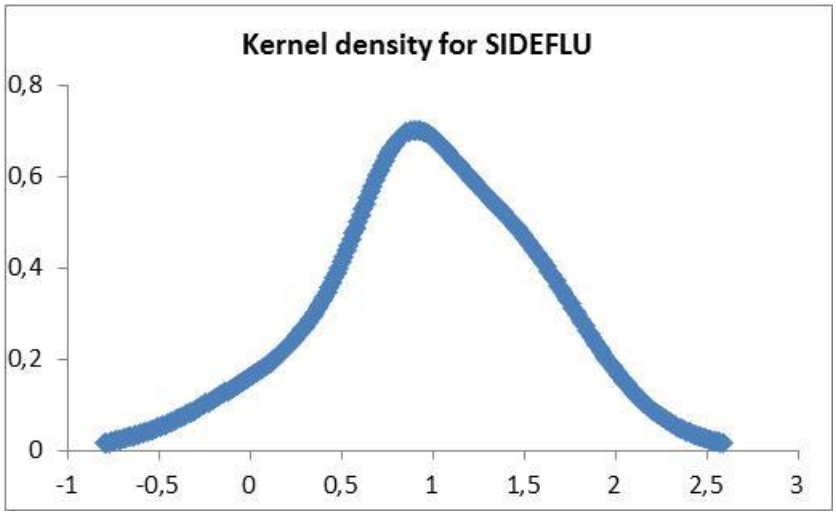

E. Yearly intravenous




F. Skin reactions



G. Flu-like symptoms



# CHAPTER 10

# GENERAL DISCUSSION

The aim of this dissertation was to review the current evidence on health technology assessment for treatment of postmenopausal osteoporosis and to provide new perspectives based on data in adherence and preference for osteoporosis medications. The increasing burden of osteoporosis and major recent innovations in osteoporosis care in the last decade [1], alongside continuing limitations in healthcare resources, justify further research into the health-economic aspects of treatment of osteoporosis. For decision makers, health technology assessment including economic evaluations provides important information that help to allocate healthcare resources. For clinicians, such studies provide additional insight into the most optimal treatment strategy for their patients and can therefore be taken into account when developing treatment strategies.

This final chapter provides first an overview of the main findings of the studies included in this dissertation. Then, it discusses some methodological considerations about these studies and, finally, it ends with a discussion on the implications of our research for clinical practice, policy decision-making and future/further research.

## MAIN FINDINGS

### *ECONOMIC EVALUATION*

The number of economic evaluations in the field of osteoporosis continues to increase [2, 3]. In *chapter 3*, we performed a systematic review of articles and published abstracts assessing the cost-effectiveness of denosumab. Denosumab is a novel agent for the treatment of postmenopausal osteoporosis that showed to be safe and effective in reducing the risk of fractures [4] and subsequently received granted marketing authorization in May 2010 in Europe. For decision makers and clinicians, it is important to understand the evidence about the societal cost-effectiveness of denosumab. Our review included four articles and eight congress abstracts published up to April 2012. When considering thresholds that are acceptable in most Western countries and especially when accounting for differences in adherence between drugs, denosumab was, in most studies, shown to be a cost-effective treatment compared with most first-line and second-line options (including generic alendronate) in the treatment of women with high fracture risk. Denosumab may therefore be considered as a first-line treatment for patients at high risk of fractures.

Since many other treatments are currently available for the treatment of osteoporosis, we appraised, in *chapter 4*, economic evaluations of all available drugs for postmenopausal osteoporosis published after 2007. A total of 39 economic evaluations were identified between 2008 and 2013. Active osteoporotic drugs are generally cost-effective compared with no treatment in postmenopausal women aged over 60-65 years with low bone mass, especially those with prior vertebral fractures. In view of the heterogeneity in fracture risk, comparators, country setting, model structure and incorporation of medication adherence, and given the lack of head-to-head comparisons, it is not yet possible to make clear recommendations between drugs in terms of cost-

effectiveness. With regard to the quality of reporting of these economic evaluations, despite the fact that guidelines for conducting health economic evaluations are widely available for many years and previous reviews have already criticized economic evaluations for poor reporting [2], we observed that quality of reporting is still largely insufficient for several articles. Improving the quality of reporting of economic evaluations (with perhaps the help of the recent CHEERS guideline [5]) and hence the overall quality of economic evaluations in osteoporosis is required.

In *chapter 5*, we extensively discussed one important consideration for cost-effectiveness analyses in the field of osteoporosis, i.e. the incorporation of medication adherence. In this chapter, we reported the substantial impact of poor adherence on cost-effectiveness ratios and discussed approaches to incorporate non-adherence and non-persistence in economic evaluations in osteoporosis. Given the large impact of poor adherence on economic results, adherence and persistence should become an integral part of future economic evaluations in the field of osteoporosis.

*ADHERENCE STUDIES*

In *chapter 6*, we assessed the clinical and economic burden of non-adherence with oral bisphosphonates in an Irish setting using a modelling approach. This analysis revealed that poor adherence reduced by approximately fifty percent the potential benefits of drug therapy observed in clinical trials and doubled the cost per quality-adjusted life-years (QALY) gained of these medications. In addition, we showed that interventions to improve medication adherence have the potential to be an efficient way of allocating healthcare resources. By example, for a hypothetical intervention that increases medication adherence by 50%, it is cost-effective (using a threshold of 45,000€ per QALY gained) to spend up to 300€ per year for such intervention. These findings emphasize the urgent need to improve adherence with osteoporosis medications and to develop and evaluate, also from the health economic perspective, adherence-enhancing interventions.

In *chapter 7*, we therefore identified studies that tested some form of patient adherence program and reported quantitative results of adherence. Several interventions were identified in 20 studies (published until June 2012) including educational programs, monitoring/supervision, different drug regimens, patient decision aid, pharmacist intervention and electronic prescription. The efficacy of education (tested in 10 studies) was variable across studies. Simplification of dosing regimens, electronic prescription, patient decision aid and pharmacist intervention were showed to increase in medication adherence but only in a limited number of studies. Monitoring and providing feedback to patients on bone marker results seems however not an effective way to enhance adherence according to 4 studies. We recommend that promising interventions should be subjected to further rigorous evaluation.

*PREFERENCE STUDIES*

Given the burden of poor adherence to oral regimens and the availability of new drug treatment with different routes and timing of administration, understanding the preferences of patients for new administration schemes could be very useful for decision-makers and health professionals. *Chapters 8* and *9* therefore contributed to the limited evidence about the preferences of patients for osteoporosis drug therapy, especially regarding new routes and timing of administration of treatment. First, a qualitative research (using the nominal group technique method) was performed to identify most important attributes for drug treatment in osteoporosis (*Chapter 8*). Based on this qualitative research, five important attributes were identified (effectiveness, side effects, mode and frequency of administration and cost) and hence included in the discrete-choice experiment (DCE).

*Chapter 9* presented the results of the DCE to assess the preferences of patients for drug therapy. This study revealed that patients, as expected, preferred treatment with higher effectiveness and lower costs, but also that patients preferred 6-month subcutaneous or oral monthly tablet compared with weekly oral tablet. Patients also disliked more being at risk of gastro-intestinal disorders than being at risk of skin reactions or flu-like symptoms. The DCE also revealed that patients are willing to pay or to give up some efficacy for their preferred treatment options. A substantial heterogeneity was observed for most parameters underlining the importance of clinical/shared decision-making taking into account individual preferences to improve osteoporosis care.

## METHODOLOGICAL CONSIDERATIONS

Different methods were used in this dissertation including systematic reviews (*chapters 3-4-7*), a modelling study (*chapter 6*), a nominal group technique (*chapter 8*) and a DCE (*chapter 9*). This section addresses strengths and limitations of these methods.

*SYSTEMATIC REVIEW*

Systematic reviews were performed to review the evidence about the cost-effectiveness of denosumab *(chapter 3)*, about recent cost-effectiveness analyses of all available drugs in osteoporosis *(chapter 4)*, and about interventions to improve medication adherence *(chapter 5)*.

By evaluating all available evidence, systematic reviews are a powerful tool to help decision makers and to identify gaps in the current literature. Guidelines to perform systematic reviews of economic evaluations in health care and in particular in searching literature databases for health care economic evaluations have been developed [6-9]. Assessing the quality of studies is also an important step in the process in systematic reviews and has gained further attention in the literature. In *chapter 3*, we used the Philips checklist [10, 11] to assess cost-effectiveness analyses of denosumab. This checklist provides a framework to assess the quality of models for the purpose of health technology assessment. In *chapter 4*, we employed the CHEERS checklist [5] in order to

assess the quality of reporting of economic evaluations. This checklist was specifically produced with the aim of harmonizing the presentation of information. It should however be acknowledged that poor reporting does not necessarily lead to poor quality or results in bias. In *chapter 7*, to assess the quality of studies assessing interventions to improve medication adherence, the so-called Delphi list was modified [12]. The initial list contains a set of generic core items for quality assessment of randomized clinical trials [12] and, for the purpose of our systematic review, elements to evaluate interventional behavioral studies were not included.

While harmonization and quality of reporting is a first necessary step towards synthetizing evidence about the cost-effectiveness of health technologies, local, i.e. context-specific, economic evaluation will still be required to provide decision makers with relevant information. The transferability of economic evaluations has been extensively discussed in the literature [13-16] and several reasons could explain potential differences in cost-effectiveness between countries including the incidence of the disease, the availability of health resources, clinical practice patterns and relative prices. To improve the comparability and quality of health economic evaluation, defining minimal methodological and structural requirements that could be transferable to any specific decision-making context is perhaps the step forward [17].

*MODELLING HEALTH AND COSTS*

In *chapter 6*, a modelling study was used to assess the clinical and economic burden of poor adherence with osteoporosis. In order to capture the long-term consequences of fractures, a lifetime modelling study is required. Modelling is a useful tool in health technology assessment allowing to synthetize information about healthcare process, to extrapolate results from clinical trials, to combine multiple sources of data and to characterize uncertainty [18]. Modelling can also be used prior to research [18] to assess the potential economic value of healthcare interventions such as adherence-enhancing interventions. Models have however limitations related to the quality of the model/assumptions and the data feeding the model [19, 20]. Models should therefore be designed to represent the complexity of the healthcare problem with the greatest precision and to remain as close as possible to real-life practices including effectiveness, adherence and safety of drugs [20]. In our study, we used a previously validated microsimulation Markov model [21]. A Markov model is appropriate to characterize disease with a recurrence of events and when the risk is continuous over time [22], which is the case for osteoporosis [23]. Most of the existing models in the field of osteoporosis are however cohort-based models [21]. The major weakness of this approach is that it does not integrate memory and thus future events do not depend on prior events [21]. By simulating patients one by point and tracking their history, microsimulation Markov model could address the above weakness and has the potential to be more accurate than cohort models, leading to higher accuracy of estimates. These models have a better ability to represent the complexity and the heterogeneity of disease such as osteoporosis and are beginning to supplant cohort-based models in

health technology assessment [24]. Discrete-event simulation could also offer an interesting framework to representing complex healthcare problems [25].

*NOMINAL GROUP TECHNIQUE*

In order to design our DCE, we first needed to identify and select attributes. Attribute development is fundamentally important to obtain reliable results but is often poorly reported in DCE in healthcare [26]. A literature review was initially performed to identify a list of potential attributes for inclusion. As this list exceeded the number of attributes that could reasonably be tested in a DCE [27], a nominal group technique was used to select the most important attributes. In our study, patients were first asked to rank a list of twelve potentially important attributes; then a group discussion took place follow by a second ranking of the same attributes. Our study *(chapter 8)* showed the feasibility of this method in prioritizing attributes for inclusion in DCE. However, although most patients changed their ranking after discussion, the nominal group technique discussions did not markedly affect rank order of preferences for the attributes in the total group when compared with rank order before discussions. Other methods (such as best-worst scaling, other rating/ranking exercises) could be alternative approaches. Further work is required on the methods for attribute selection for DCE and on the value of the nominal group technique for that purpose. Such studies will of course be hampered by the difficulty to identify the 'gold standard' of what will be the real attributes that subjects take into account in various situations of choices.

*DISCRETE-CHOICE EXPERIMENT*

DCEs are increasingly used to elicit preferences in health and healthcare [28, 29]. DCEs quantify the relative importance of various attributes that characterize an health intervention and allows to evaluate the trade-offs that respondents make between them [30]. As the number of DCE in health care is increasing rapidly, guidelines for conducting discrete-choice experiments have been developed [27, 31]. Advanced methods for selecting attributes and levels [26], for constructing experimental design [32] and for statistical analyses [27] have been developed. DCE, as a stated-preference method, has however been criticised because they may not predict real behaviours and choices [33]. There has been limited testing of external validity [28]. Such tests are however difficult to conduct given market imperfection in health care.

## IMPLICATIONS FOR DECISION MAKING, CLINICAL PRACTICE AND FUTURE/FURTHER RESEARCH

The findings of this dissertation have several implications for decision making, clinical practice and future/further research. This chapter describes these implications.

### DECISION MAKING

First, cost-effectiveness analyses are increasingly used in reimbursement decisions. Most countries now require economic evaluations as part of the reimbursement process. Cost-effectiveness is therefore considered as the fourth hurdle to market access besides quality, safety and efficacy [34, 35]. Reviewing the evidence about the cost-effectiveness of (new) drugs in osteoporosis (*chapters 3 and 4)* could therefore be very useful to help decision makers making decisions about these (new) drugs.

Second, *part II* of this dissertation raised awareness about the urgent need to improve adherence and the potential economic value of improving adherence. Decision makers should take initiatives to tackle this important problem in the management of osteoporosis. Developing (cost-) effective interventions to enhance adherence would therefore be worthwhile [36].

Third, *chapters 8 and 9* suggested that osteoporotic patients have preferences for medication attributes. These findings could be useful for decision making (especially drug reimbursement) where insights into the preferences of patients groups should be taken into account alongside medical and economic considerations [37]. How to integrate evidence on patient preferences in healthcare decision making is however unclear and requires further investigation [38].

### *CLINICAL PRACTICE*

First, as physicians' decisions plays a key role in health care spending, it is important that physicians take into account both costs and effects of health interventions and hence help delivering health care in an efficient, i.e. cost-effective way. Physicians should therefore understand the relevance of cost-effectiveness analyses for healthcare delivery, know how to judge the quality of economic evaluations and have an understanding on the evidence about the cost-effectiveness of drugs.

Second, our findings suggest that poor adherence is a major hurdle in osteoporosis management. Improving medication adherence is therefore urgently needed. Clinicians should be aware of the problem of poor adherence and set up interventions/programs to improve adherence. Enhancing adherence is however a complex issue. Several (intentional and unintentional) reasons of poor adherence have been identified in the literature [39]. A recent direction in efforts to improve patient adherence is to develop interventions tailored to the individual. When messages included in health education programs are adapted to characteristics, needs, and interests of the individual, the messages provided during the intervention will be more relevant, less redundant and more likely to be read, saved, remembered and adhered to. An important problem in translating intention to behavioral change is that many individuals, in the end, do not achieve the desired change. Hence, informing patients in a neutral and balanced way, e.g. by applying patient decision aids and shared decision making, which may consequently result in goal setting by identifying and setting clear

action plans is important to translate intentions into actions. Action plans refer to specific strategies (sub-behaviors) aimed at realizing steps within specific periods of time in order to be able to perform the ultimate desired behavior. One of the challenges of such program was seen in the sustainability of such change and a need for long term additional support initiatives.

Third, information about patients' preferences may help physicians to improve patient satisfaction and adherence with therapy. The substantial heterogeneity in patients' preferences for medication attributes highlights the importance to take into account individual preferences into clinical/shared decision-making to improve osteoporosis care. Relying solely on collective-level approaches to explore individual patient preferences will probably be insufficient to optimise medical doctors' sensitivity to preferences of the individual and unique patient during a consultation. Informing individual patients about alternative options and their outcomes, and involving them in decision making, would be very important to improve patient's satisfaction and the outcome of medical care [40]. Patient decision aids have already been shown to improve the quality of clinical decisions about osteoporosis medications and may help to improve adherence [40].

*FUTURE/FURTHER RESEARCH*

Our study gives several directions for future/further cost-effectiveness analyses. First, poor adherence represents a new perspective on health economic assessment in osteoporosis and our studies could provide relevant background for incorporating medication adherence and persistence. Second, quality of reporting of economic evaluations is still insufficient for several recent cost-effectiveness studies. We recommend that the CHEERS guideline serves as a reference for reporting economic evaluations in osteoporosis. Third, the comparability of economic evaluations remains difficult since they differ according to modelling, comparators and populations. Defining minimal methodological and structural requirements for any osteoporotic model would certainly be interesting. In addition, more attention should be given to the methods used for the identification and synthesis of clinical effectiveness data, especially now there is an increasing need for comparative cost-effectiveness studies. All these steps will help to improve our ability to synthesize evidence across (health economic) studies and improve the quality of decision making.

Developing (cost-) effective interventions to enhance adherence would also be extremely worthwhile. Promising programs should be the subject to further rigorous clinical (and economic) evaluation. Eliciting patients' preferences is becoming an interesting approach to include the patient perspective but few considerations about the transferability of patients' preferences are currently available in the literature. International comparison of patients' preferences for osteoporosis medications would definitely be interesting. The development and evaluation of a patient decision aid to promote shared-decision making could also be interesting to improve osteoporosis care. A patient decision aid may result in patients, that are well-informed and involved deliberately choice for a certain drug, showing higher motivation and therefore adherence to the drug of first choice.

Patient decision aids may also have a counter effect, being that patients less often choose for starting on a drug regime in the first place.

In this dissertation, we provided new perspectives to health technology assessment in osteoporosis from adherence and preference studies. Poor adherence to medication affects many other diseases including hypertension, HIV infection or psychiatric illness [41]. Understanding the economic implications of poor adherence, assessing the value of improving adherence and further evaluation of programs to enhance adherence would also be required in all these diseases. In addition, given the potential increasing role of preferences in clinical and policy decisions, understanding patients' preferences for health and healthcare would also be worthwhile in many disease areas.

## REFERENCES


1. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, 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.
2. Fleurence RL, Iglesias CP, Torgerson DJ. Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. Osteoporos Int. 2006;17(1):29-40.
3. Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. Osteoporos Int. 2014;25(1):51-60.
4. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.
5. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.
6. Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. JAMA. 2002;287(21):2809-12.
7. Sassi F, Archard L, McDaid D. Searching literature databases for health care economic evaluations: how systematic can we afford to be? Med Care. 2002;40(5):387-94.
8. Alton V, Eckerlund I, Norlund A. Health economic evaluations: how to find them. Int J Technol Assess Health Care. 2006;22(4):512-7.
9. Vale L, Thomas R, MacLennan G, Grimshaw J. Systematic review of economic evaluations and cost analyses of guideline implementation strategies. Eur J Health Econ. 2007;8(2):111-21.
10. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics. 2006;24(4):355-71.
11. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004;8(36):iii-iv, ix-xi, 1-158.
12. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 1998;51(12):1235-41.
13. Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M, et al. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res. 2011;3:89-104.
14. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009;12(4):409-18.

15. Knies S, Ament AJ, Evers SM, Severens JL. The transferability of economic evaluations:testing the model of Welte. Value Health. 2009;12(5):730-8.
16. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride JE. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. Curr Med Res Opin. 2007;23(4):671-82.
17. van Haalen HG, Severens JL, Tran-Duy A, Boonen A. How to select the right cost-effectiveness model? : A systematic review and stepwise approach for selecting a transferable health economic evaluation model for rheumatoid arthritis. Pharmacoeconomics. 2014;32(5):429-42.
18. Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? Pharmacoeconomics. 2000;17(5):445-59.
19. Sheldon TA. Problems of using modelling in the economic evaluation of health care. Health Econ. 1996;5(1):1-11.
20. Soto J. Health economic evaluations using decision analytic modeling - Principles and practices-utilization of a checklist to their development and appraisal. Int J Technol Assess Health Care. 2002;18(1):94-111.
21. Hiligsmann M, Ethgen O, Bruyere O, Richy F, Gathon HJ, Reginster JY. Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. Value Health. 2009;12(5):687-96.
22. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993;13(4):322-38.
23. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis--a review of the literature and a reference model. Osteoporos Int. 2007;18(1):9-23.
24. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics. 2006;24(11):1043-53.
25. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Moller J, et al. Modeling using Discrete Event Simulation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4. Value in Health. 2012;15(6):821-7.
26. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. Health Econ. 2012;21(6):730-41.
27. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health. 2011;14(4):403-13.
28. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ. 2012;21(2):145-72.
29. Marshall D, Bridges JF, Hauber B, Cameron R, Donnalley L, Fyie K, et al. Conjoint Analysis Applications in Health - How are Studies being Designed and Reported?: An Update on Current Practice in the Published Literature between 2005 and 2008. Patient. 2010;3(4):249-56.
30. Ryan M. Discrete choice experiments in health care. BMJ. 2004;328(7436):360-1.

31. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics. 2008;26(8):661-77.
32. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Muhlbacher A, Regier DA, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health. 2013;16(1):3-13.
33. Lagarde M, Blaauw D. A review of the application and contribution of discrete choice experiments to inform human resources policy interventions. Hum Resour Health. 2009;7.
34. Taylor RS, Drummond MF, Salkeld G, Sullivan SD. Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. Bmj. 2004;329(7472):972-5.
35. Rawlins MD. Crossing the fourth hurdle. Br J Clin Pharmacol. 2012;73(6):855-60.
36. Hiligsmann M, Boonen A. The need for (cost)-effective interventions to enhance adherence with osteoporosis medications. Curr Med Res Opin. 2014;30(2):297-9.
37. Hiligsmann M, Kanis JA, Compston J, Cooper C, Flamion B, Bergmann P, et al. Health technology assessment in osteoporosis. Calcif Tissue Int. 2013;93(1):1-14.
38. Dirksen CD, Utens CM, Joore MA, van Barneveld TA, Boer B, Dreesens DH, et al. Integrating evidence on patient preferences in healthcare policy decisions: protocol of the patient-VIP study. Implement Sci. 2013;8:64.
39. Jones TJ, Petrella RJ, Crilly R. Determinants of persistence with weekly bisphosphonates in patients with osteoporosis. J Rheumatol. 2008;35(9):1865-73.
40. Montori VM, Shah ND, Pencille LJ, Branda ME, Van Houten HK, Swiglo BA, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. Am J Medicine. 2011;124(6):549-56.
41. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-97.

# LIST OF PUBLICATIONS OF THE THESIS

**Hiligsmann M**, Kanis JA, Compston J, Cooper C, Flamion B, Bergmann P, Body JJ, Boonen S, Bruyere O, Devogelaer JY, Goemaere S, Kaufman JM, Rozenberg S, Reginster JY (2013) Health technology assessment in osteoporosis. *Calcified Tissue International*, 93(1), 1-14

**Hiligsmann M**, Ben Sedrine W, Boonen A, Dirksen C & Reginster JY (2013). Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporotic women. *Expert Review of Pharmacoeconomics & Outcomes research*, 13(1), 19-28

**Hiligsmann M**, Ben Sedrine W, Wyers C, Evers S, Kanis JA, Reginster JY, Silverman S, Raemakers B, Boonen A (2015). A systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis. *PharmacoEconomics* [Epub Ahead of Print]

**Hiligsmann M**, Boonen A, Rabenda V, Reginster JY (2012) The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. *Expert Review of Pharmacoeconomics & Outcomes research*, 12(2), 159-66.

**Hiligsmann M**, McGowan, Bennett K, Barry M & Reginster JY (2012). The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. *Value in Health*, 15(5), 604-12.

**Hiligsmann M**, Salas M, Hughes DA, Manias F, Gwadrhy-Sridhar F, Link P, Cowell W (2013). Interventions to improve osteoporosis medication adherence and persistence: A systematic review and literature appraisal by the ISPOR medication adherence & persistence special interest group. *Osteoporosis International*, 24(12), 2907-18

**Hiligsmann M**, van Durme C, Geusens P, Dirksen C, Dellaert B, van der Weijden T, Reginster JY, Boonen A (2013). Nominal group technique to select attributes for discrete choice experiments. An example for drug treatment choices in osteoporosis. *Patient Preference & Adherence*, 7, 133-9.

**Hiligsmann M** , Dellaert B, Dirksen C, van der Weijden T, Reginster JY, Goemaere S, Watson V, Boonen A. (2014) Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. *Arthritis Research & Therapy*, 16(1):R36.

**Hiligsmann M**, Boonen A. (2014) The need for (cost)-effective interventions to enhance adherence with osteoporosis medications, Current Medical Research & Opinion, 30(2), 297-9 (Editorial)

# VALORISATION

This dissertation aimed to review cost-effectiveness analyses of drugs in osteoporosis, to assess the burden of medication non-adherence and effectiveness of programs to enhance adherence, and to evaluate the preferences of patients for medication attributes. All these studies could be useful for decision makers and clinicians in efforts to optimize the management of osteoporosis, while considering efficient allocation of scarce healthcare resources. An efficient prescription of medications, the development of programs to enhance adherence and a better incorporation of preferences in policy and clinical decision making could definitely be useful in tackling the increasing burden of osteoporosis. In addition, our research could serve as case to raise awareness of the general population on the importance of medication adherence in other diseases. Although more research is needed to further explore effectiveness and efficiency of programs to improve adherence, and to decide how we can adequately incorporate a patient's preference in clinical decisions, several societal, economic and clinical implications of the research from this dissertation are already discussed in this chapter.

## SOCIETAL IMPLICATIONS

Osteoporosis is an increasingly major public health problem. In western countries, at least one in three women and one in five men over 60 years will suffer from an osteoporotic fracture during their remaining lifetime [1]. Osteoporotic fractures results in significant morbidity, mortality, and reductions in quality of life. In the Netherlands, a recent report by the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA) [2] estimated that approximately 76,000 new fragility fractures were sustained in 2010 and the economic burden of incident and previous fragility fractures was estimated at €824 million for the same year. Moreover, with increasing life expectancy, it is estimated that the number of fractures will even increase by 40% in 2025 [2].

Reducing the burden of osteoporosis by optimizing the management of osteoporosis is therefore becoming very important. This dissertation identified several directions for a better management of osteoporosis. First, we highlighted the substantial clinical and economic burden of non-adherence with osteoporosis medications. Improving adherence is therefore urgently needed and should be (or become) a priority for decision makers and healthcare professionals. Several promising interventions to enhance adherence such as education program or electronic monitoring were identified in a systematic review. We also showed that patients expressed preferences for medication attributes such as mode of administration and potential side effects and revealed a substantial heterogeneity in patients' preferences. Promoting shared-decision making by incorporating the patient's preference in decision making could certainly be useful to optimize osteoporosis management.

## ECONOMIC IMPLICATIONS

Considering limited healthcare resources available, it is becoming increasingly important for decision makers to make efficient decisions. Assessing the cost-effectiveness of health interventions is therefore needed to help decision makers and could in fine lead to optimizing the management of osteoporosis and reducing the burden of the disease. This dissertation included several analyses about the economic value of anti-osteoporosis medications that could be useful and used by decision makers. By example, two reviews of recent cost-effectiveness analysis of drugs were performed suggesting that new drugs (such as denosumab) could represent an efficient way of allocating healthcare resources. Another analysis revealed the potential economic value of adherence-enhancing interventions, suggesting that designing and implementing programs to improve adherence could be efficient.

## CLINICAL IMPLICATIONS

Alongside societal and economic implications, this dissertation should alert clinicians that manage patients with osteoporosis in daily management of osteoporosis. By improving insight into factors that contribute to the clinical and economic burden of osteoporosis, our studies make clear that clinicians should take care of the adherence of their patients. The variation in the patients' preferences for medication attributes observed in our research highlighted the importance to take into account individual preferences into clinical decision-making to improve osteoporosis care. A first step might be to raise awareness of the avoidable burden by improving adherence and the potential role of education and patient preference.

## REFERENCES

1. Hiligsmann M, Bruyere O, Ethgen O, Gathon HJ, Reginster JY. Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women. Bone. 2008;43(6):991-4.
2. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, 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). Archives of osteoporosis. 2013;8(1-2):136.

# SUMMARY

Osteoporosis is a bone disease leading to increased fracture risk affecting more than one in three women aged over 60 years in western countries. With the rapid development of new anti-osteoporosis medications in a context of limited healthcare resources, it is important to help decision makers to make appropriate and efficient decisions about the use of these medications. Health technology assessment (HTA) aims to assess the medical, social, economic and ethical implications of health technologies, and is therefore extremely useful to inform and guide health policy decisions. In particular, economic evaluations that compare health technologies in terms of costs and outcomes are increasingly used to promote a more rational use of health resources. In recent years, non-adherence with osteoporosis medications has emerged as a critical obstacle in the treatment of osteoporosis but relatively few studies have been conducted to assess the economic implications of poor adherence and to estimate the effectiveness and potential economic value of programs to enhance adherence. To improve medication adherence, understanding the preferences of patients and addressing patients' concerns with treatment would be worthwhile.

The increasing burden of osteoporosis and major recent innovations in osteoporosis care, alongside continuing limitations in healthcare resources, justified further research into the health-economic aspects of treatment of osteoporosis. The aim of this dissertation was therefore to review economic evidence on the treatment of osteoporosis and to provide new perspectives from adherence and preference studies. More specifically, the first part of the thesis reviewed and critically appraised studies about the cost-effectiveness of drugs in postmenopausal women. The second part assessed the economic implications of poor adherence with anti-osteoporosis medications, estimated the potential economic value of improving adherence and reviewed the published literature about interventions to improve adherence. The last part, finally, evaluated the preferences of patients for osteoporosis medication attributes and established how patients trade between these attributes.

Chapter 2 of the thesis provides a general overview of HTA including economic evaluations and reviews the various aspects of HTA in osteoporosis, including epidemiology and burden of disease, and assessment of the cost-effectiveness of recent advances in the treatment of osteoporosis. Chapters 3 and 4 present systematic literature reviews and critical appraisal of cost-effectiveness analyses about different drugs in osteoporosis such as denosumab. These reviews suggest that osteoporotic drugs are generally cost-effective compared to no treatment in postmenopausal women aged over 60-65 years with low bone mass, especially those with prior vertebral fractures. We also observed that quality of reporting is still largely insufficient for several cost-effectiveness articles. In chapter 5, the importance of incorporating medication adherence in cost-effectiveness analysis in osteoporosis was described, explained and justified.

The next two chapters focus on medication adherence. First, chapter 6 assessed the clinical and economic burden of non-adherence with oral bisphosphonates using a modelling approach. This analysis revealed that poor adherence may reduce the potential benefits of drug therapy observed in

clinical trials by approximately fifty percent and doubles the cost per quality-adjusted life-years gained of these medications. In addition, this study suggests that interventions to improve medication adherence have the potential to increase efficiency in allocating healthcare resources. Chapter 7 reviewed and appraised published articles that tested adherence improvement programs, suggesting that several interventions (including education programs, monitoring/supervision, different drug regimens) could represent an effective way to improve adherence.

Finally, chapters 8 and 9 provided evidence on the preferences of patients for osteoporosis medications. Given the burden of poor adherence to oral regimens and the availability of new drug treatment with different routes and timing of administration, understanding the preferences of patients for new administration schemes could be useful for decision-makers and health professionals. In chapter 8, a qualitative research (using the nominal group technique method) was performed to identify most important attributes for drug treatment in osteoporosis. Based on this qualitative research, five important attributes were identified (effectiveness, side effects, mode and frequency of administration and cost) and hence included in the discrete-choice experiment (DCE). Chapter 9 reported the results of the DCE conducting in a sample of 257 Belgian women, revealing that patients have preferences for mode of administration (such as 6-month subcutaneous or oral monthly tablet) and that they are willing to pay or to give up some efficacy for their preferred treatment options. A substantial heterogeneity was also observed for most parameters underlining the importance of shared decision-making and taking into account individual preferences.

The findings of this dissertation can have several implications for decision making, clinical practice and future/further research. First, the review of economic evidence about anti-osteoporosis drugs could help decision makers to efficiently allocate healthcare resources. Second, this dissertation raises awareness about the urgent need to improve adherence among those patients that have deliberately chosen for a drug regimen, after having been well-informed on the pros and cons per treatment option, and the potential economic value of improving adherence. Decision makers and clinicians have to tackle the problem of poor adherence and set up interventions/programs to improve adherence. Third, information about patients' preferences may help physicians to improve patient satisfaction and adherence with therapy while the substantial heterogeneity in patients' preferences for medication attributes highlights the importance to take into account individual preferences into shared decision-making to improve osteoporosis care. Finally, this dissertation could give several directions for future/further research including the importance to improve the quality of reporting of economic evaluations but also to incorporate medication adherence in cost-effectiveness analyses, the need to develop (cost-) effective interventions to enhance adherence, and the importance to understand and incorporate patients' preferences in clinical and policy decisions.

# WORDS OF THANKS

Four years ago, I had the opportunity to start a second PhD trajectory. This was a wonderful experience to enrich my knowledge, to enlarge my expertise area and to develop a network of contact. This dissertation is the output of this work and results from the contribution and support of many people. I am extremely grateful to all the people that participated in the success of this project.

First, I would like to immensely thank Annelies, my promotor. This project would not have been possible without your help in the development, design and conduct of this research. Many thanks for your continuous support, availability and for sharing your knowledge with me. You will always remain an example for me and your devotion to your work is something incredible. I also thank a lot Trudy and Carmen, my other promotors for sharing their field of research and knowledge as well as for their availability, encouragements and contribution to this dissertation. A special thanks also for Benedict that plays a key role in the design of the preference project. Benedict, you are a great professional and I fully understand your decision. I look forward to future collaborations with all of you.

This project would also not have been possible without the financial support of Amgen and I am extremely grateful for your support and the freedom in performing research. I remember the lunch at the Radisson Hotel in Athens where Enkhe, Sean and Matt let me know their interest to support our idea being a starting point in this project. Many thanks also to Michele for being the contact person from Amgen the last years.

Many people have also contributed to this dissertation. In total, 35 people have co-authored the articles of this thesis! I thank you all for your help in conducting the studies and reviewing the articles. Special thanks for Prof Jean-Yves Reginster who initiated me to the world of osteoporosis and to Verity for important input in our preference research. Two studies were performed among international working groups and I am also grateful the Belgian Bone Club and the ISPOR Medication Adherence Special Interest Group for making these projects feasible. I also take the opportunity to thank all anonymous reviewers and editors that played an important role in the quality of the published articles and the evaluation committee for showing their interest in this research by accepting the task to review and taking time for this underestimated role.

I am also extremely grateful to the department of Health Services Research and in particular to Silvia, Aggie and Dirk that gave me the opportunity to complete this PhD and for their confidence. My biggest pride today is to be appointed as assistant professor and having the opportunity to teach and share my knowledge with young researchers. I am proud to have received your confidence and to perform everyday my dream work. I am also looking forward to be soon in the other side of a PhD defense as co-promotor and I wish already all success to Charles, Inge, Kei Long, Monika, Rana… and I hope much more in the future.

Last but not least, the success of my professional work would not have been as good without the support and compassion of my family and especially my wife Sophie. Many thanks for your support and understanding during extra working hours! Finally, I dedicated in 2010 my first PhD thesis to Emy-Lise (my first daughter). I will therefore dedicate this second thesis to my second daughter, Eloïse. We will have only two children…

Mickael

# CURRICULUM VITAE

## ABOUT THE AUTHOR

Mickael Hiligsmann was born on August 18th, 1981, in Verviers, Belgium. After completing his secondary education, he studied Economics at the University of Liege (Belgium), for which he obtained his Master degree in June 2003. Between July 2003 and December 2010, he worked as teaching assistant at the Department of Economics of the HEC-School of Management of the University of Liege, Belgium. During this period, he obtained a Master in Public Health Sciences (2006) and a Master in Pedagogy in Economics (2006), both from the University of Liege. In February 2010, he obtained a PhD in medical sciences for a thesis about the development and validation of Markov microsimulation model for the economic evaluation of osteoporosis management and several applications related to screening and treatment of osteoporosis. Between January 2011 and December 2012, he was appointed as post-doc researcher at the Departments of Internal Medicine and of Clinical Epidemiology and Medical Technology Assessment from Maastricht University, the Netherlands. Since January 2013, Mickael has been appointed as assistant professor in health economics and health technology assessment (HTA) at the Department of Health Services Research of Maastricht University. In addition to teaching activities, Mickael is currently involved in several HTA projects and is co-promoter of 5 PhD students.

As a researcher, Mickael has experience in health economic evaluation including cost-effectiveness analyses, decision-analytic modelling and quality of life studies. He has also gained expertise in stated-preference methods such as discrete-choice experiments and best-worst scaling, and he conducted several work in the field of medication adherence. Mickael applied all these economic methods to several topics in primary and clinical care as well as public health, and he also addressed methodological issues related to these methods. On January 2015, Mickael has co-authored 57 peer-reviewed articles. Among these, he has been the first author of 33 peer-reviewed articles including several publications in PharmacoEconomics, Value in Health, European Journal of Public Health, Health Policy, Expert Review of Pharmacoeconomics & Outcomes Research, Arthritis Care & Research, Arthritis Research & Therapy, Journal of Bone & Mineral Research, Bone, Osteoporosis International, Patient Preference & Adherence, etc. He is currently member of the editorial board of Expert Review of Pharmacoeconomics & Outcomes Research, Journal of Medical Economics, Advances in Therapy and Archives of Public Health, and has acted as reviewer for about twenty-five international journals or organizations. He is also member of the scientific committees of the International Osteoporosis Foundation (IOF) and of the European Society of Clinical and Economic Aspects of Osteoporosis (ESCEO) and part of the ISPOR Medication Adherence Special Interest Group and of the ISPOR Medical Nutrition Special Interest Group. On January 2015, Mickael has an H-Index of 16 (Web of Science).

## PEER-REVIEWED ARTICLES

**Hiligsmann M**, Evers SM, Ben Sedrine W, Wyers C, Kanis JA, Reginster JY, Silverman S, Raemakers B, Boonen A (2015). A systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis. *PharmacoEconomics* [Epub Ahead of Print]

Peters EG, Smeets B, Dekkers M, Buise MD, de Jonge WJ, Slooter GD, de Reilingh TS, Wegdam JA, Nieuwenhuijzen G, Rutten H, de Hingh I, **Hiligsmann M**, Buurman WA, Luyer M. The effects of stimulation of the autonomic nervous system via perioperative nutrition on postoperative ileus and anastomotic leakage following colorectal surgery (SANICS II trial): a study protocol for a double-blind randomized controlled trial. *Trials* [Epub Ahead of Print]

**Hiligsmann M**, Ben Sedrine W, Bruyère O, Evers SM, Rabenda V and Reginster JY (2015) Cost-effectiveness of vitamin D and calcium supplementation in the treatment of elderly women and men with osteoporosis. *European Journal of Public Health,* 25(1), 20-5

Evers SM, **Hiligsmann M**, Adarkwah C (2015) Risk of bias in trial-based economic evaluation. Health & Psychology, 30(1), 52-71

**Hiligsmann M**, Cooper C, Arden N, Boers M, Branco JC, ML Brandi ML, Bruyère O, Guillemin F, Hochberg MC, Hunter DJ, Kanis JA, Kvien TK, Laslop A, Pelletier JP, Pinto D, Reiter-Niesert S, Rizzoli R, Rovati LC, Severens JL, Silverman S, Tsouderos Y, Tugwell P, Reginster JY. (2014) A reference case for economic evaluations in osteoarthritis. An Expert consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (2014) *Seminars in Arthritis and Rheumatism,* 44(3), 271-82

Kruger L, Evers SM, **Hiligsmann M**, Wild C (2014) Divergent evidence requirements comparing the authorization and reimbursement processes of high-risk medical devices - The European situation. *Health Policy and Technology*, 3(4), 253-264

Kanis JA, **Hiligsmann M** (2014) The application of health technology assessment in osteoporosis. *Best Practice & Research Clinical Endocrinology & Metabolism*, 28(6), 895-910

Bavesh J, **Hiligsmann M**, Mathews J and Evers SM (2014) A Stakeholder Analysis for Advancing Health Technology Assessment in India. *Value in Health Regional Issues,* 3, 167-71

Rizzoli R, Branco J, Brandi ML, Boonen S, Bruyère O, Cacoub P, Cooper C, Diez-Perez A, Duder J, Fielding RA, Harvey NC, **Hiligsmann M**, Kanis JA, Petermans J, Ringe JD, Tsouderos Y, Weinman J, Reginster JY (2014) Management of osteoporosis of the oldest old. Osteoporosis International, 25(11), 2507-29

Wijnen BF, de Kinderen RJ, Colon AJ, Dirksen CD, Essers BA, **Hiligsmann** M, Leijten FS, Ossenblok PP and Evers SM (2014) Eliciting patients' preferences for epilepsy diagnostics: a discrete choice experiment. *Epilepsy & Behavior*, 31C, 102-9

**Hiligsmann M** , Dellaert B, Dirksen C, van der Weijden T, Reginster JY, Goemaere S, Watson V, Boonen A (2014) Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. *Arthritis Research & Therapy,* 16(1):R36

**Hiligsmann M**, Boonen A (2014) The need for (cost)-effective interventions to enhance adherence with osteoporosis medications, *Current Medical Research & Opinion*, 30(2), 297-9 (Editorial)

**Hiligsmann M**, Cooper C, Arden N, Boers M, Branco JC, Luisa Brandi M, Bruyère O, Guillemin F, Hochberg MC, Hunter DJ, Kanis JA, Kvien TK, Laslop A, Pelletier JP, Pinto D, Reiter-Niesert S, Rizzoli R, Rovati LC, Severens JL, Silverman S, Tsouderos Y, Tugwell P, Reginster JY (2013). Health economics in the field of osteoarthritis: An Expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Seminars in Arthritis and Rheumatism*, 43(3), 303-13

**Hiligsmann M**, Salas M, Hughes DA, Manias F, Gwadrhy-Sridhar F, Link P, Cowell W (2013). Interventions to improve osteoporosis medication adherence and persistence: A systematic review and literature appraisal by the ISPOR medication adherence & persistence special interest group. *Osteoporosis International*, 24(12), 2907-18

**Hiligsmann M**, Kanis JA, Compston J, Cooper C, Flamion B, Bergmann P, Body JJ, Boonen S, Bruyere O, Devogelaer JY, Goemaere S, Kaufman JM, Rozenberg S, Reginster JY (2013) Health technology assessment in osteoporosis. *Calcified Tissue International*, 93:1-14.

**Hiligsmann M**, Ben Sedrine W, Bruyère O, Reginster JY (2013). Cost-effectiveness of strontium ranelate in the treatment of male osteoporosis. *Osteoporosis International*, 24, 2291-300

**Hiligsmann** M, van Durme C, Geusens P, Dirksen C, Dellaert B, van der Weijden T, Reginster JY, Boonen A (2013). Nominal group technique to select attributes for discrete choice experiments. An example for drug treatment choices in osteoporosis. *Patient Preference & Adherence*, 7, 133-9

**Hiligsmann M**, Ben Sedrine W, Reginster JY (2013) Cost-effectiveness of bazedoxifene compared with raloxifene in the treatment of postmenopausal osteoporotic women. *Journal of Bone and Mineral Research, 28, 807-15*

**Hiligsmann M**, Ben Sedrine W, Boonen A, Dirksen C & Reginster JY (2013). Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporotic women. *Expert Review of Pharmacoeconomics & Outcomes research*, 13, 19-28

Bruyère O, **Hiligsmann M**, Zegels B, Neuprez A, Reginster JY. (2013). Risk of hip fracture in community-dwelling and institutionalized osteoporotic patients: a 3-year study. *International Journal of Gerontology*, 7, 167-170

Bruyère O, Foss M, Zegels B, Leonori L, **Hiligsmann M**, Neuprez A, Reginster JY (2013). Comparison of the proportion of patients potentially treated with an anti-osteoporotic drug using current criteria of the Belgian national social security and the new suggested FRAX criteria. *Rheumatolology International*, 33, 973-978.

Kanis JA, Adachi JD, Cooper C, Clark P, Cummings SR, Diaz-Curiel M, Harvey N, **Hiligsmann M**, Papaioannou A, Pierroz DD, Silverman SL, Szulc P (2013). Standardising the descriptive epidemiology of osteoporosis: recommendations from the Epidemiology and Quality of Life Working Group of IOF. *Osteoporosis International*, 24(11):2763-4

**Hiligsmann M**, McGowan, Bennett K, Barry M & Reginster JY (2012). The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. *Value in Health*, 15, 604-12.

**Hiligsmann M**, Boonen A, Rabenda V, Reginster JY (2012). The importance of integrating medication adherence in pharmacoeconomic analyses: the example of osteoporosis, *Expert Review of Pharmacoeconomics & Outcomes Research*, 12, 159-66

**Hiligsmann M**, Bruyère O, Roberfroid D, Dubois C, Detilleux J, Gillet P, Parmentier Y, Carton J, Reginster JY (2012). Trends in hip fracture incidence and in the prescription of anti-osteoporosis medications during the same time period in Belgium (2000-2007). *Arthritis Care & Research*, 64, 744-50.

Kanis JA, Reginster JY, Kaufman JM, Ringe J, Adachi JD, **Hiligsmann M**, Rizzoli R, & Cooper C (2012). A reappraisal of generics bisphosphonates in osteoporosis, *Osteoporosis International*, 23, 213-21.

Fischer M, Lekeu F, Quittre A, Olivier C, Wojtasik V, Gillain D, **Hiligsmann M**, Salmon E. (2012). [Proof of concept of a cost-utility analysis for treatment by cognitive rehabilitation in early dementia] *Revue de Neuropsychologie*, 4, 151-62 (Article in French)

**Hiligsmann M** & Reginster JY (2012). [A changing medical and economic world: complex diseases and interest in economic evaluation of health technologies]. *Revue Médicale de Liège*, 67, 258-62 (Article in French)

**Hiligsmann M** & Reginster JY (2011). Cost-effectiveness of denosumab compared with oral bisphosphonates in the treatment of Belgian postmenopausal osteoporotic women, *PharmacoEconomics*, 29(10), 895-911

Kanis JA, Cooper C**, Hiligsmann M**, Rabenda V, Reginster JY & Rizzoli R (2011). Partial adherence: a new perspective on health economic assessment in osteoporosis, *Osteoporosis International*, 22, 2565-73

Johansson H, Kanis JA, McCloskey E, Oden A, Devogelaer JP, Kaufman J, Neuprez A, **Hiligsmann M**, Bruyère O & Reginster JY (2011). A FRAX model for the assessment of fracture probability in Belgium, *Osteoporosis International*, 22, 453-61

**Hiligsmann M**, Vanoverberghe M, Neuprez A, Bruyère O & Reginster JY (2010). Cost-effectiveness of strontium ranelate for the prevention and treatment of osteoporosis, *Expert Review of Pharmacoeconomics & Outcomes Research*, 10, 359-66

**Hiligsmann M** & Reginster JY (2010). Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women, *Bone*, 47, 34-40

**Hiligsmann M**, Rabenda V, Bruyère O & Reginster JY (2010). The clinical and economic burden of nonadherence with oral bisphosphonates in osteoporotic patients, *Health Policy*, 96, 170-77.

**Hiligsmann M**, Gathon HJ, Bruyère O, Ethgen O, Rabenda V & Reginster JY (2010). Cost-effectiveness of osteoporosis screening followed by treatment: the impact of medication adherence, *Value in Health*, 13, 394-401

**Hiligsmann M**, Rabenda V, Gathon HJ, Bruyère O & Reginster JY (2010). Potential clinical and economic impact of non-adherence with osteoporosis medications, *Calcified Tissue International*, 86, 202-210

**Hiligsmann M**, Bruyère O & Reginster JY (2010). Cost-effectiveness of strontium ranelate versus risedronate in the treatment of postmenopausal osteoporotic women aged over 75 years, *Bone*, 46, 440-446

**Hiligsmann M**, Bruyère O & Reginster JY (2010). Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women, *Osteoporosis International*, 21, 157-165.

Reginster JY, **Hiligsmann** M & Bruyère O (2010). Strontium ranelate: long-term efficacy against vertebral, non-vertebral and hip fracture in patients with postmenopausal osteoporosis, *Therapeutic Advances in Musculoskeletal Disease*, 2, 133-423

Scholtissen S, Bruyère O, Neuprez A, Severens JL, Herrero-Beaumont G, Rovati L, **Hiligsmann M** & Reginster JY (2010). Glucosamine sulfate in the treatment of knee osteoarthrithis: cost-effectiveness comparison with acetaminophen, *International Journal of Clinical Practice*, 64, 756-62

Reginster JY, Neuprez A, **Hiligsmann M** & Bruyère O (2010). Oral calcitonin in the management of osteoarthrithis: hope or fantasy? *International Journal of Clinical Rheumatology*, 25, 53-58

**Hiligsmann M**, Ethgen O, Bruyère O, Richy F, Gathon HJ & Reginster JY (2009). Development and validation of a microsimulation Markov model for the evaluation of treatments for osteoporosis, *Value in Health*, 12, 687-696.

Bruyère O, Scholtissen S, Neuprez A, **Hiligsmann M** & Reginster JY (2009). Impact of chondroitin sulfate on health utility in patients with knee osteoarthritis: towards economic analysis, *Journal of Medical Economics*, 12, 356-360

Reginster JY, **Hiligsmann M,** Rabenda V, Zegels B, Neuprez A & Bruyère O (2009). Ibandronate in the management of postmenopausal osteoporosis, *Clinical Medicine: Therapeutics*, 1, 1409-1421

Reginster JY, Deroisy R, Neuprez A, **Hiligsmann M**, Zegels B & Bruyère O (2009). Strontium ranelate: new data on fracture prevention and mechanisms of action, *Current Osteoporosis Reports*, 7, 96-102

Bruyère O, Roces Varela A, Adami S, Detilleux J, Rabenda V, **Hiligsmann M** & Reginster JY (2009). Loss of hip bone mineral density over time is associated with spine and hip fracture incidence in osteoporotic postmenopausal women, *European Journal of Epidemiology*, 24, 707-712.

Rabenda V, **Hiligsmann M** & Reginster JY (2009). Poor adherence to oral bisphosphonates treatment and its consequences: a review of the evidence, *Expert opinion on pharmacotherapy*, 10, 2303-2315.

Neuprez A, Johansson H, Kanis JA, McCloskey E, Oden A, Bruyere O, **Hiligsmann M**, Devogelaer JP, Kaufman J, Reginster JY (2009). [A FRAX model for the assessment of fracture probability in Belgium]. *Revue Médicale de Liège*, 64, 612-619 (Article in French)

**Hiligsmann M**, Ethgen O, Bruyère O & Reginster JY (2008). An economic evaluation of quantitative ultrasound as prescreening test for the identification of osteoporotic patient, *Disease Management & Health Outcomes*, 16, 429-438

**Hiligsmann M**, Bruyère O, Ethgen O, Gathon HJ & Reginster JY (2008). Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women, *Bone*, 43, 991-994

**Hiligsmann M**, Ethgen O, Richy F & Reginster JY (2008) Utility values associated with osteoporotic fracture: a systematic review of the literature, *Calcified Tissue International*, 82, 288-292

Neuprez A, **Hiligsmann M**, Scholtissen S, Bruyère O & Reginster JY (2008). Strontium ranelate: the first agent of a new therapeutic class, in osteoporosis, *Advances in therapy*,25:1235-56

**Hiligsmann M**, Bruyère O, Pire G & Reginster JY (2008). [Economic evaluation of osteoporosis screening strategy conducted in the Province of Liège with the cooperation of Liège Province Santé], *Revue Médicale de Liège*, 63, 588-594 (Article in French)

**Hiligsmann M**, Bruyère O & Reginster JY (2008). [Long-term risk of osteoporotic fracture in Belgium], *Revue Médicale de Liège*, 63, 480-487 (Article in French)

Neuprez A, **Hiligsmann M**, Bruyère O & Reginster JY (2008). [Anti-fracture efficacy of intravenous ibandronate : how to translate epidemiological studies into daily clinical practice], *Revue Médicale de Liège*, 64, 525-529 (Article in French)

Neuprez A, **Hiligsmann M**, Bruyère O, Ethgen O & Reginster JY (2007). Prevention of hip fractures in osteoporosis, *Minerva ortopedica e traumatologica*, 58, 423-438