Volume 13 • Number 4 • 2010
VALUE IN HEALTH

Cost–Effectiveness of Osteoporosis Screening Followed by Treatment: The Impact of Medication Adherence

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ABSTRACT

Objective: To estimate the impact of medication adherence on the cost–effectiveness of mass-screening by bone densitometry followed by alendronate therapy for women diagnosed with osteoporosis.

Methods: A validated Markov microsimulation model with a Belgian health-care payer perspective and a lifetime horizon was used to assess the cost per quality-adjusted life year (QALY) gained of the screening/treatment strategy compared with no intervention. Real-world adherence to alendronate therapy and full adherence over 5 years were both investigated. The real-world adherence scenario employed adherence data from published observational studies, and medication adherence was divided into persistence, compliance, and primary adherence. Uncertainty was investigated using one-way and probabilistic sensitivity analyses.

Results: At 65 years of age, the costs per QALY gained because of the screening/treatment strategy versus no intervention are €32,008 and €16,918 in the real-world adherence and full adherence scenarios, respectively. The equivalent values are €80,836 and €40,462 at the age of 55 years, and they decrease to €10,600 and €1229 at the age of 75 years. Sensitivity analyses show that the presence of the upfront cost of case finding has a substantial role in the impact of medication adherence on cost–effectiveness.

Conclusion: This study indicates that nonadherence with osteoporosis medications substantially increases the incremental cost–effectiveness ratio of osteoporosis screening strategies. All aspects of medication adherence (i.e., compliance, persistence, and primary adherence) should therefore be reported and included in pharmacoeconomic analyses, and especially in the presence of the upfront cost of case finding (such as screening cost).

Keywords: adherence, compliance, cost–effectiveness, osteoporosis, persistence, screening.

Introduction

Medication nonadherence is a widespread public health problem, especially in chronic diseases such as osteoporosis. Approximately 75% of women who initiated osteoporosis drug therapy were shown to be nonadherent with treatment within 1 year, and almost 50% discontinued therapy by this time [1]. Poor adherence to drug therapy is associated with adverse outcomes, and nonadherent patients have a significantly greater risk of fractures [2,3]. Such behavior may have a substantial impact on the cost–effectiveness of interventions [4,5] and, in particular, for screening strategies which include the upfront cost of case finding.

Screening for osteoporosis has been widely recommended for identifying patients at high risk before any fracture occurs [6]. The cost–effectiveness of screening strategies is of obvious importance, and many studies have been reported in the literature [7]. These studies have mainly investigated the cost–effectiveness of bone densitometry combined with therapy [8–10], of prescreening strategies for bone densitometry (e.g. quantitative ultrasound or clinical risk factors) [11,12], and of strategies assessing absolute fracture risk combining clinical risk factors with bone densitometry [13–17].

Poor adherence to osteoporosis drug therapy was not routinely included by these studies despite its potential impact. Moreover, when adherence was included, a lack of methodological rigor and consistency in definitions reduced the impact of medication nonadherence. Some studies did provide realistic assumptions with respect to persistence with drug therapy [8,10], but additional adherence effects (such as inappropriate use of drug therapy or primary nonadherence) were largely neglected. These problems may result in the overestimation of the cost–effectiveness of osteoporosis screening [8].

In light of these limitations, this study aimed to evaluate the impact of all aspects of medication nonadherence (i.e., noncompliance, nonpersistence, and primary nonadherence) on the cost–effectiveness of osteoporosis screening. Using our validated Markov microsimulation model, recently published in *Value in Health* [18], we estimated the cost per quality-adjusted life year (QALY) gained of bone densitometry combined with alendronate therapy for those who have osteoporosis, compared with no intervention. We also assessed the impact of the upfront cost of case finding on the effect of medication adherence on cost–effectiveness. Bone densitometry is the most widely used and recommended instrument to establish or confirm a diagnosis of osteoporosis [6]. Despite the new World Health Organization paradigm of treating osteoporosis based on absolute fracture risk rather than bone density alone [19], bone densitometry remains a vital component in the diagnosis and management of osteoporosis [20]. In Belgium, the reference country for the analysis, as in many other European countries, drug therapy is actually only reimbursed for patients with a bone mineral density (BMD) *t*-score ≤ -2.5, defined by bone densitometry, or in the presence of one or more fragility fracture.

Methods

Defining Adherence

Because a wide variety of definitions for medication adherence are used in the literature [4,21], there is a need to define the terminology. Recently, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication

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10.1111/j.1524-4733.2009.00687.x

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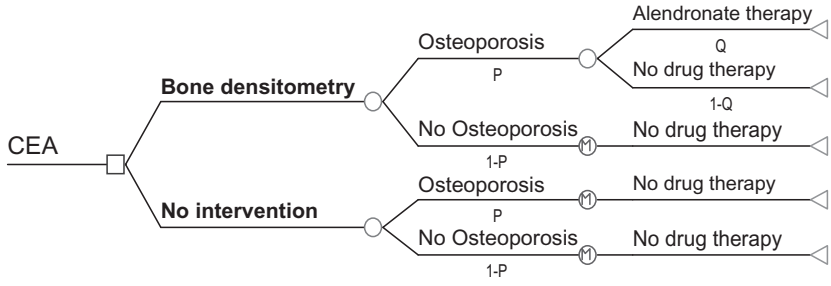

Figure 1 Model structure. *p* represents the prevalence of osteoporosis and *q* the rate of primary adherence. CEA, Cost–effectiveness analysis.

Compliance and Persistence Workgroup set out definitions [22]. Medication adherence is a general term encompassing different aspects explained below, i.e., persistence, compliance, and primary adherence.

Medication persistence is defined by ISPOR as "the length of time from initiation to discontinuation of therapy" [22]. It may be reported as the proportion of patients still taking medication at the end of a predefined time period. Medication compliance is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing of regimen" [22]. It is often reported as the number of doses taken in relation to the dispensing period, often called the "medication possession ratio (MPR)" [22]. Primary nonadherence, frequently mentioned in the literature [6,23], is assumed for patients diagnosed with osteoporosis but who did not take any medication.

Screening/Treatment Strategy

A decision analytic model was used to compare the screening/treatment strategy with no intervention (Fig. 1). The screening/treatment strategy consisted of bone densitometry combined with a 5-year alendronate therapy for women diagnosed with osteoporosis (BMD *T*-score ≤ -2.5) and who are primary adherent. Prevalence of osteoporosis was derived from the recommended National Health and Nutrition Examination Survey (NHANES) III [24] reference database and the proportions of women diagnosed as having osteoporosis were therefore 6.95%, 15.07%, and 28.96%, respectively for those aged 55, 65, and 75 years. The cost of bone densitometry measurement was estimated at €47 per patient (in 2006) and included the dual-energy x-ray absorptiometry cost (€27) and one physician visit (€20) [11].

Economic Model

A Markov microsimulation model using decision analysis software (TreeAgePro 2006 Suite, release 0.4, TreeAge Software, Inc., Williamstown, MA) was used to estimate the cost–effectiveness of the screening/treatment strategy compared with no intervention. The model development and validation was recently published in *Value in Health* [18]; and the model was previously used to estimate the effects of changes in baseline population risk and changes in life expectancy on absolute lifetime fracture risks [25].

The model health states were no fracture, death, hip fracture, clinical vertebral fracture, forearm fracture, and other fracture. The cycle length of the model was 1 year and the model followed the patients individually until they died or reached the age of 105 years. The required time horizon to fully evaluate the benefit of a particular intervention should be very long because fractures have long-term impact on quality of life and are associated with long-term costs. The use of a lifetime horizon has therefore been recommended for health economic analyses conducted in osteoporosis [26]. The patient history was recorded by so-called "tracker" variables and thus, prior fractures and current residential status (either in the community or in a nursing home) were used in calculations of transition probabilities, effectiveness, and costs. All the women began in the state "no fracture" and all the transitions between health states were possible in each cycle and regardless of the current state. Each state has its associated costs and effectiveness, depending on the patient history.

The current study was performed from a health-care payer perspective including direct health-care costs paid by the compulsory national health insurance and the patient's out-of-pocket contribution, in line with the Belgian methodological guidelines for pharmacoeconomic evaluations [27]. Transition cost included direct fracture costs in the year following the fracture and long-term cost beyond the first year for women entering a nursing home after a hip fracture. An adjustment was made to take into account that women might be institutionalized later in life in any case, regardless of their hip fracture [18]. Effectiveness was expressed in QALYs, which is an attractive outcome measurement in the field of osteoporosis because it offers the advantage of capturing the benefits from reductions in both morbidity and mortality [28]. The disutility associated with fractures was modeled as a relative reduction in QALY [29]. In accordance with Belgian methodological guidelines for pharmacoeconomic evaluations [27], discount rates of 3% and 1.5% were assumed for cost (expressed in 2006) and effectiveness, respectively. For a detailed description and explanation of the model and data, please refer to the published paper [18].

Fracture Risk

In the base-case analysis, we investigated women without prior fracture. In order to accurately reflect the fracture risk of women with osteoporosis (i.e., BMD *T*-score ≤ -2.5), the estimated incidence rates of first fracture in Belgium [25] were adjusted using a previously described and validated method [30]. This method calculates the relative risk of individuals below the threshold value compared with that of the general population.

The number of standard deviations of BMD below the age-matched average BMD was derived from the recommended NHANES III [24] database, in which young adult bone mineral density values were not significantly different from Belgian estimates [31]. 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, forearm, and other osteoporotic fractures, respectively [32]. The relative risk for hip fracture was shown to decrease with age and ranged from 3.68 at 50 years, to 1.93 at 85 years [33].

Alendronate Therapy

We assumed that treated women received a 5-year alendronate therapy, the most widely prescribed osteoporosis treatment,

worldwide. The clinical effectiveness of alendronate in the treatment of women with osteoporosis has been extensively documented. A recent meta-analysis was conducted for the National Institute for Health and Clinical Excellence appraisal and included large randomized controlled trials and therefore women aged between 55 years to 81 years at baseline with severe osteoporosis, osteoporosis, and osteopenia [34]. The relative risks versus placebo were 0.62 (95% CI 0.40–0.96) for hip fracture, 0.55 (95% CI 0.40–0.66) for clinical vertebral fracture, 0.85 (95% confidence interval [CI] 0.67–1.09) for forearm fracture, and 0.83 (95% CI 0.74–0.93) for other fracture. These relative risks were selected for all age groups and the effect of treatment was assumed to persist for a duration (i.e., offset-time) equal to the duration of therapy, in line with clinical studies [35,36] and assumptions used in previous models [9,37,38]. The risk reduction was assumed to decline linearly to zero during this period.

The cost of treatment included drug costs and costs of assessment. The annual cost of alendronate therapy was estimated at €308.3 (Fosamax [Merck & Co., Whitehouse Station, NJ], €70.94 for a package of 12, 70-mg tablets, once per week [39]). Most of the women treated with alendronate therapy received calcium and vitamin D supplementation [40,41]. We therefore included the cost of calcium and vitamin D (Steovit D3 [Nycomed, Brussels, Belgium], 500 mg calcium and 400 IU vitamin D, €14.99 for 60 tablets, once per day [42]). In accordance with previous standard assumptions regarding the monitoring of osteoporotic treatments [28], we assumed that treatment was associated with one yearly general practitioner's visit (€20) and one bone densitometry measurement every second year (estimated at €47) [11]. No adverse events were assumed in the base-case analysis, because the overall safety profile of alendronate is favorable [6].

Adherence Data

Clinical effectiveness and drug costs are affected by poor compliance and failure to persist with therapy. Adherence to alendronate therapy (daily and weekly combined) in real-life setting was derived from a recent published Belgian study [2], the reference country for the analysis. For modeling purposes, adherence was divided into primary adherence, persistence, and compliance.

First, primary nonadherence was estimated at 11.6% in a published Belgian study [43]. This study showed that only 88.4% of women initiated any medication after a diagnosis of osteoporosis. Primary nonadherent patients were assumed to only incur the cost of screening.

Then, 42.5% of those who initiated treatment discontinued it within 6 months [2]. For these women, no treatment effect was assumed, and we assigned 3 months of therapy cost, as previously suggested [23]. Another 18.1%, 13.9%, and 7.2% of women dropped off therapy at 1-year, 2-year, and 3-year, respectively. Therefore, only 18.2% of the women received a 5-year treatment. It was assumed that if patients discontinue therapy, they received no further treatment and offset-time for nonpersistent patients was the same as the duration on therapy.

Finally, women taking medication were considered to be compliant if their MPR was at least 80% in any given year and poorly compliant otherwise. An MPR $\geq$ 80% was most commonly used to define high compliance [44]. The probabilities of being less than 80% compliant were estimated at 23.9%, 4.0%, and 1.2% in the first, second, and following years of treatment, respectively [2]. These women benefit from a lower treatment efficacy. Poor compliance (MPR < 80%) was associated with a 35% increase in hip fracture rate (relative risk [RR] = 1.35, 95% CI 1.17–1.56) in line with the Belgian study [2]. Because this study did not assess the relationship between compliance and non–hip fractures, we assumed a conservative [44] 17% increase in other fractures rates (RR = 1.17, 95% CI 1.09–1.25) [45], for poorly compliant women. The relative risks from the systematic review were applicable to the population with a compliance of 80% or greater. So, for example, if alendronate was assumed to reduce the risk of hip fracture by 38%, then compliant women would experience a 38% reduction in hip fractures while noncompliant women would experience only a 16% ($0.62 \times 1.35 = 0.837$) reduction in hip fractures. For poorly compliant women, drug cost was reduced by 20%.

Because adherence rates differ between jurisdictions [44,46,47], additional analyses were conducted assuming that adherence rates were 20% and 40% higher than in the real-world scenario. In other terms, the probabilities of being primary nonadherent and poorly compliant, and the dropout rates in the real-world setting were reduced by 20% and 40%, respectively.

Presentation of Results and Sensitivity Analyses

For each analysis, the incremental cost–effectiveness ratio (ICER) was computed as the difference between the screening/treatment strategy and no intervention in terms of total costs divided by the difference between them in terms of effectiveness, expressed in accumulated QALYs. A total of 200,000 first-order Monte Carlo simulations were deemed sufficient to ensure stability of the results. An ICER represents the cost of the screening/treatment strategy per one QALY gained, compared with no intervention. Although the ICER is increasingly used in the decision-making progress, there is no consensus on the cost per QALY that represents acceptable value for money. Decision-making process depends on many elements other than cost–effectiveness, such as preferences or budget impact. Belgian decision-makers have therefore not defined threshold values below which an intervention can be considered cost–effective [48].

ICER was estimated for real-world adherence to alendronate therapy and for full adherence over 5 years (to estimate the theoretical potential). One-way and probabilistic sensitivity analyses were performed to investigate the uncertainty related to assumptions and model parameters on the results of the base-case analysis. One-way sensitivity analyses assessed the impact of variations in single parameter and base-case assumption. Discount rates, fracture disutility, fracture cost, fracture risk, therapy cost, treatment efficacy, and offset time were varied over plausible ranges. Reductions in nonadherence rates were also tested, as well as changes in specific aspects of medication adherence (i.e., compliance, persistence, primary adherence, or the increase in fracture rates for poorly compliant women). One-way sensitivity analyses were also conducted assuming the cost of generic alendronate (i.e., Beenos [Mithra, Brussels, Belgium], €37.8 for a package of 12, 70-mg tablets, once per week [39]). Additional variation of screening cost per patient was assumed to cover changes in the cost of bone densitometry but also, indirectly, uncertainty around osteoporosis prevalence rates in the target populations.

Probabilistic sensitivity analyses assessed the effects of uncertainty in all model parameters simultaneously. Lognormal distributions were assumed for the relative fracture risks of women with osteoporosis, of alendronate therapy and of noncompliant women, as recommended by Briggs's book for relative risk parameters [49]. A uniform distribution was also assumed for the cost of screening with a range from 70% to 130% of the base value. Distributions for other parameters have been published elsewhere [18]. Cost–effectiveness acceptability curves were then constructed from the incremental cost and QALYs of the screening/treatment strategy in comparison with no intervention

Table 1 Lifetime costs, QALYs, and ICER (cost in € per QALY gained) of the screening/treatment strategy versus no intervention, according to screening age and medication adherence

		Screening/treatment strategy	
	No intervention	Real-world adherence	Full adherence
Aged 55 years			
Costs (€)	10,288.0	11,515.0	12,326.4
QALYs	18.0509	18.0661	18.1013
ICER, €/QALY		80,836	40,462
Aged 65 years			
Costs (€)	11,561.6	12,227.4	12,656.2
QALYs	12.9312	12.9520	12.9959
ICER, €/QALY		32,008	16,918
Aged 75 years			
Costs (€)	11,120.0	11,291.7	11,178.3
QALYs	8.0289	8.0451	8.0763
ICER, €/QALY		10,600	1,229

ICER, incremental cost–effectiveness ratio; QALY, quality-adjusted life year.

for 150 second-order Monte Carlo simulations. They show the probability that the screening/treatment strategy is cost–effective compared with no intervention as a function of the thresholds willingness to pay per QALY.

Results

The lifetime costs, QALYs, and the ICER for the screening/treatment strategy versus no intervention are shown in Table 1, according to age and medication adherence. In the case of real-world adherence, the QALY gains of the screening/treatment strategy compared with no intervention were estimated at 0.0152, 0.0208, and 0.0163 at the ages of 55, 65, and 75 years, respectively. These values represented only 30.2%, 32.1%, and 34.2% of the one estimated with full adherence assumption. The cost per QALY gained for the screening/treatment strategy was shown to progressively decrease with increasing age of screening and to be highly sensitive to medication adherence. At the ages of 55 and 65 years, the ICERs of the screening/treatment strategy were approximately doubled under real-world adherence when compared with full adherence.

Assuming a 20% increase in adherence rates reduced the cost per QALY gained of the screening/treatment strategy at €63,482, €25,416, and €6379 at the ages of 55, 65, and 75 years, respectively (Fig. 2). The equivalent values decreased to €54,000, €22,723, and €4258 when assuming an increase of 40%. If we assumed the cost of generic alendronate, the ICER of the screening/treatment strategy at 65 years of age was €20,055 and €6322 in the real-world adherence and full adherence scenarios, respectively (Fig. 3). The equivalent values were €65,236 and €28,505 at the age of 55 years, and the screening/treatment strategy was cost-saving (i.e., lower cost and higher effectiveness) at the age of 75 years, even in the case of real-world adherence.

The impact of additional one-way sensitivity analyses on the ICER were conducted at the age of 65 years (Table 2). Each aspect of medication adherence was specifically assessed. The ICER was markedly reduced when assuming full persistence and no changes in compliance and primary nonadherence rates; while the cost–effectiveness was less sensitive to changes in compliance or in primary adherence. The increase in fracture rates for poorly compliant women had a limited impact on the results. Other one-way sensitivity analyses showed moderate increases in the cost per QALY gained with assumed lower fracture disutility, lower fracture costs and more marked increases with higher discount rates, lower fracture risk, higher therapy cost, and lower treatment efficacy (Table 2). Although model parameters and treatment specificities had an impact on the ICER of the screening/treatment strategy, they did not significantly influence the relative difference between real-world and full adherence.

Screening cost had a large impact on the effect of medication adherence on the ICER of the screening/treatment strategy (Fig. 4). At the screening age of 65 years, the ratio between real-world and full adherence, estimated at 1.89 (= 32,008/16,918), in the base-case analysis, decreased to 1.62 if screening cost was reduced by 50% and increased to 2.09 for a 50% increase of screening cost. When assuming no upfront fixed cost of case-finding, the ratio decreased to 1.35.

The probability that the screening/treatment strategy was cost-effective compared with no intervention increased with increasing age of screening and with improving medication adherence (Fig. 5). At a willingness to pay of €40,000, the screening/treatment strategy had a probability of being cost–effective respectively of 79.3%, 59.3%, and 2.7% at the ages of 75, 65, and 55 years in the case of real-world adherence. The equivalent probabilities were 88.7%, 90.7%, and 40.7% under full adherence assumption. The probabilities that the screening/treatment strategy was cost-saving were 15.3% and 42.7% at the age of 75 years, respectively, in the case of real-world and full adherence.

Discussion

Medication nonadherence has important negative consequences for clinical outcomes as well as for cost–effectiveness, and, in

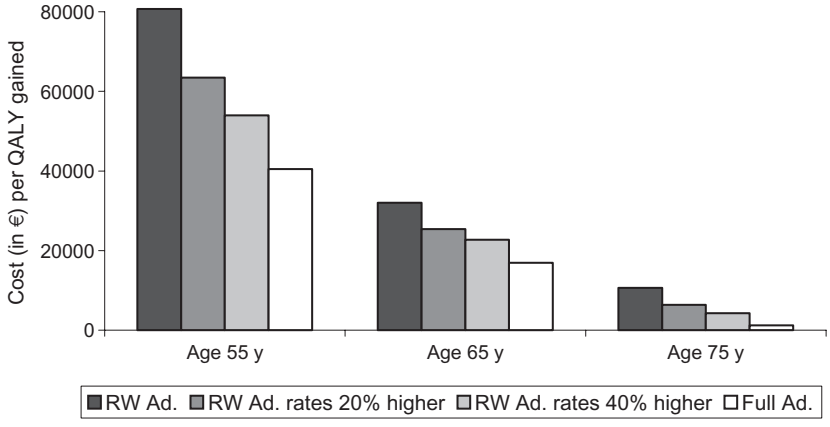

Figure 2 Impact of medication adherence on the incremental cost–effectiveness ratio (cost in € per QALY gained) of the screening/treatment strategy versus no intervention. Ad., adherence; QALY, quality-adjusted life year; RW, real-world.

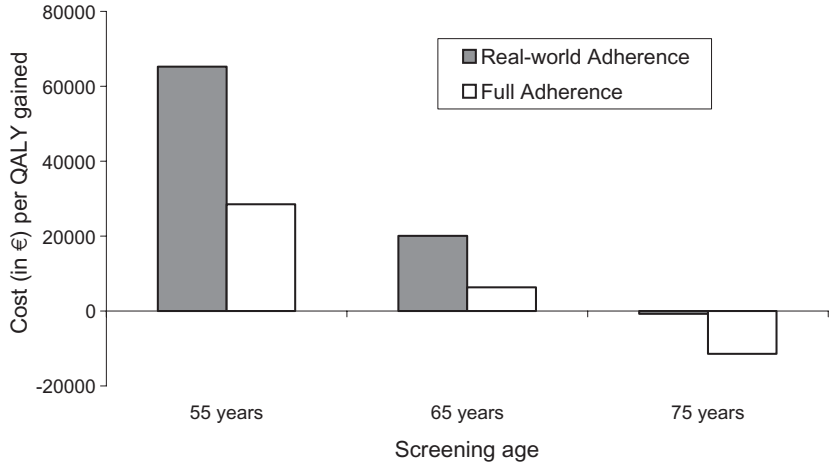

Figure 3 Incremental cost–effectiveness ratio (cost in € per QALY gained) of the screening/treatment strategy versus no intervention, assuming the cost of generic alendronate. QALY, quality-adjusted ife year.

Table 2 One-way sensitivity analyses of incremental cost-effectiveness ratio (cost in € per quality-adjusted life-year gained) of the screening/treatment strategy versus no intervention, for women aged 65 years

Parameter	Real-world adherence	Full adherence
Base-case	32,008	16,918
Adherence		
Full primary adherence*	30,040	—
Full compliance*	30,542	—
Full persistence*	20,794	—
A 17% increase in fracture rates for poor compliance*	31,246	—
A 35% increase in fracture rates for poor compliance*	32,491	—
Model parameters		
Discount rates 3% (costs and effects)	38,424	19,308
Discount rates 5% (costs and effects)	54,921	28,771
0.75 times base-case fracture risk	52,014	29,958
1.25 times base-case fracture risk	20,320	8,982
0.75 times base-case fracture disutility	39,529	20,863
1.25 times base-case fracture disutility	25,546	14,672
0.75 times base-case fracture cost	37,042	20,156
1.25 times base-case fracture cost	26,250	11,827
0.75 times base-case therapy cost	22,122	8,317
1.25 times base-case therapy cost	40,375	22,301
0.75 times base-case treatment efficacy	52,838	30,614
1.25 times base-case treatment efficacy	20,589	8,888
0.50 times base-case offset time	41,893	22,165
1.50 times base-case offset time	26,923	10,874

*Other aspects of medication adherence are unchanged.

particular, for screening strategies which include the upfront cost of case-finding. The present study shows that poor adherence with drug therapy significantly reduces the clinical and economic outcomes of osteoporosis screening strategy. The QALY gain in the case of real-world adherence represents only 30–35% to that estimated with full adherence and the cost per QALY gained of screening strategy versus no intervention was approximately doubled when assuming real-world adherence compared with full adherence. Sensitivity analyses showed that the presence of the upfront cost of case-finding has a substantial role on the effect of medication nonadherence on ICER; hence, making ICER, in this study, highly sensitive to medication adherence through the cost of screening.

The impact of medication nonadherence on the cost–effectiveness of osteoporosis screening strategy was greater than those reported by prior studies. For example, a Swiss-based study [8] showed that the ICER of a screening strategy was CHF (Swiss franc)45,545 and CHF55,533 for women aged 65 years under full and realistic persistence assumption, respectively. For US men aged 80 years [10], the cost per QALY gained of bone densitometry and treatment strategy was $33,128 and $45,587 with full and realistic adherence assumption. This is because prior studies have not taken into account all aspects of medication adherence, rather than because of unusual medication adherence rates in the present analysis. Most of the prior studies assumed a significant level of medication nonpersistence [7], but additional adherence effects (such as imperfect use of drug therapy or primary nonad-

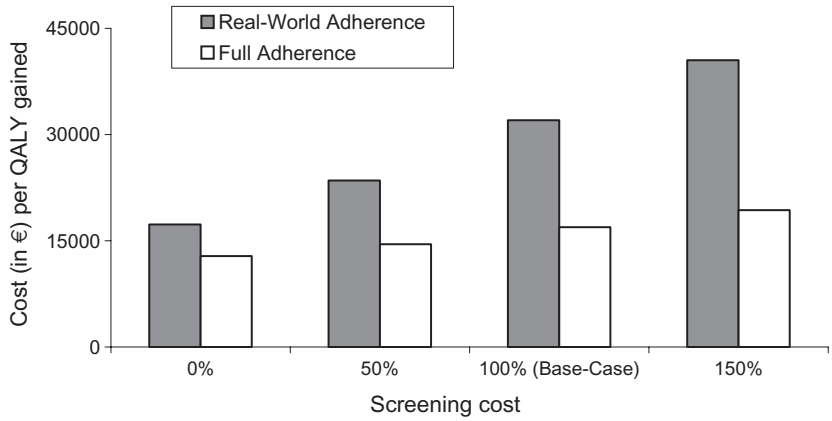

Figure 4 Incremental cost–effectiveness ratio (cost in € per QALY gained) of the screening/treatment strategy versus no intervention according to screening cost, for women aged 65 years. QALY, quality-adjusted life year.

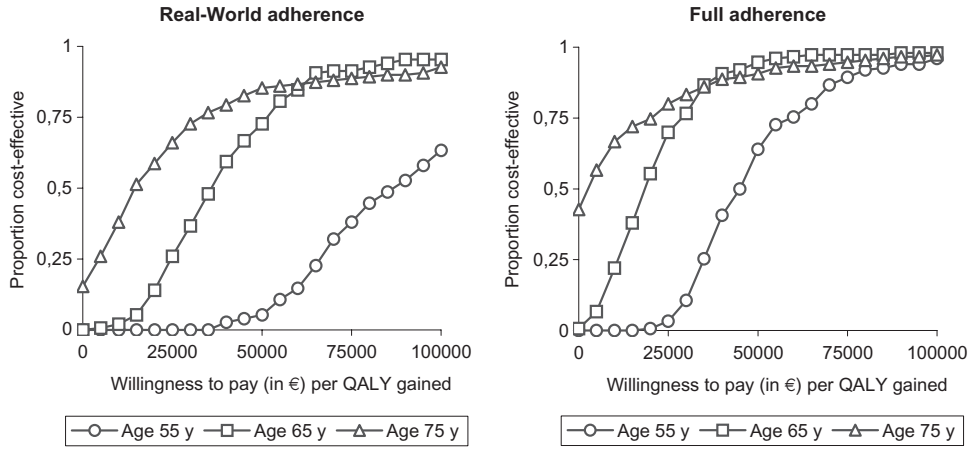

Figure 5 Cost–effectiveness acceptability curves of the screening/treatment strategy versus no intervention, according to age and medication adherence. RW, real-world; QALY, quality-adjusted life year.

herence) were largely neglected. Our study assessed all aspects of medication adherence (i.e., persistence, compliance, and primary adherence). Although persistence was shown to have the greater impact on cost–effectiveness, compliance and primary adherence have also a substantial impact on ICER and should be reported and incorporated into health economic analyses.

Improving adherence with osteoporosis medications is therefore needed to improve the cost–effectiveness of osteoporosis screening strategy. However, this is a complex and challenging issue [50]. No clear trends regarding successful interventions have been identified [50] and interventions that improve adherence are rarely cost-free. New formulations and dosages schemes (i.e., monthly oral medication, or quarterly, twice-yearly or yearly intravenous infusion) have been recently developed, which in principle can improve adherence [51]. Less frequent dosing regimens have been frequently associated with better adherence [52]. The recent introduction of generic alendronate, by decreasing the financial burden placed on the payer, may also contribute to improve the cost–effectiveness of the screening/treatment strategy, if the clinical efficacy, safety, and adherence of generic alendronate will match those of branded alendronate.

The methodology to incorporate adherence into modeling was conceptually close to the one suggested by Ström et al. [23], with some remarkable difference. In modeling compliance, patients were classified as compliant (MPR $\geq$ 80%) and poorly compliant (MPR < 80%). The proportions of these groups were derived for any given year [2] and poorly compliant patients were assumed to be associated with an increased risk of fractures [2,45]. Drug cost was also reduced for the poorly compliant group.

Our results should be analyzed in the light of these limitations, including assumptions on medication adherence. First, patients were assumed to be poorly compliant if their MPR was below 80%. This group will be, by definition, diverse in their levels of compliance, which would influence the effect of therapy on fracture risk and the cost of therapy. A vast majority of poorly compliant patients had an MPR between 50% and 80% [2] and were therefore not divided into smaller intervals. Second, drug cost was assumed to be 100% and 80% of full price for compliant and poorly compliant women, respectively. However, it is likely that some patients in both groups will not bear all these costs. Because the mean MPR was not available in these groups, we conservatively assumed high drug cost. Third, no further treatment was assumed for patients who discontinued therapy. A refill gap period of 5 weeks was used in the observational study to assess persistence [2], which is among the longest refill gap periods used in previous studies [44]. However, we cannot exclude that some patients would return to therapy after this period. A recent study identified particular patients who return from temporary interruptions in therapy [53]. Such patients may affect the results but are difficult to include in modeling because the effectiveness of oral bisphosphonates used in an intermittent regimen is unknown. Finally, differences in methodology and in patients demographics incorporated in the available studies resulted in wide variations in reported adherence data [47]. Country-specific data are therefore required because many determinants affected by local conditions may influence adherence rates [54].

Our study was constructed in line with the actual reimbursement of osteoporosis drug therapy in Belgium as well as in many European countries (i.e., women with a BMD *T*-score ≤ -2.5 or in the presence of prior fragility fracture). The screening/treatment strategy was close to that recently reported by Schwenkglenks et al. [8] and Schousboe et al. [9]. Our results were entirely consistent with these studies and with the recommendations of the National Osteoporosis Foundation recommending the prescription of bone densitometry in all women over age 65 [20].

Potential limitations may, however, be related to the study design. First, the prevalence of osteoporosis in the target population (i.e., women without fracture) was assumed to be the same than in the general women population. However, particularly in those aged 75, a substantial proportion of women with early-onset osteoporosis will already have fractured or will be treated, and the remaining population may differ with respect to osteoporosis prevalence. Although the impact may not be huge, it will be higher at an older age and the cost–effectiveness differences between screening ages may be overestimated. Second, treatment length was restricted to a 5-year period, corresponding to the duration of most clinical trials. Effectiveness and adherence over a longer period is uncertain and should be assessed in clinical trials. Finally, many other screening programs are currently available. Among those, the new World Health Organization algorithm (FRAX) recommends to guide treatment decision based on absolute fracture risk combined bone densitometry with clinical risk factors, rather than bone density alone [19]. In

the context of this paradigm, bone densitometry may have a more restricted role, but is nonetheless likely to be important for some subsets of the population [7] and remains a vital component in the diagnosis and management of osteoporosis [20]. Further cost–effectiveness modeling studies will be useful in defining the most cost–effective way bone densitometry can be used to identify patient who are likely to benefit from therapy [7]. Such analyses should definitely take into account of medication adherence, given their potential impact.

Conclusion

The results of this analysis show that nonadherence with osteoporosis medications significantly reduces the clinical and economic outcomes of osteoporosis screening strategies. All aspects of medication adherence (i.e., compliance, persistence and primary adherence) should therefore be reported and included in pharmacoeconomic analyses, and especially in the presence of upfront cost of case finding (such as screening cost).

Source of financial support: This study was performed as part of the PhD of Mickaël Hiligsmann. No sources of funding were used to assist in the preparation of this manuscript. The model development and validation was previously supported by an ESCEO-Amgen Fellowship grant received at the 6th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (Vienna 2006).

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