REVIEW ARTICLE

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A Review of the Cost Effectiveness of Bisphosphonates in the Treatment of Post-Menopausal Osteoporosis in Switzerland

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Abstract

The economic burden associated with osteoporosis is considerable. As such, cost-effectiveness analyses are important contributors to the diagnostic and therapeutic decision-making process. The aim of this study was to review the cost effectiveness of treating post-menopausal osteoporosis with bisphosphonates and identify the key factors that influence the cost effectiveness of such treatment in the Swiss setting.

A systematic search of databases (MEDLINE, EMBASE and the Cochrane Library) was conducted to identify published literature on the cost effectiveness of bisphosphonates in post-menopausal osteoporosis in the Swiss setting. Outcomes were compared with similar studies in Western European countries.

Three cost-effectiveness studies of bisphosphonates in this patient population were identified; all were from a healthcare payer perspective. Outcomes

showed that, relative to no treatment, treatment with oral bisphosphonates was predicted to be cost saving for most women aged ≥70 years with osteoporosis or at least one risk factor for fracture, and cost effective for women aged ≥75 years without prior fracture when used as a component of a population-based screen-and-treat programme. Results were most sensitive to changes in fracture risk, cost of fractures, cost of treatment, nursing home admissions and adherence with treatment. Swiss results were generally comparable to those in other European settings. Assuming similar clinical efficacy, lowering treatment cost (through the use of price-reduced brand-name or generic drugs) and/or improving adherence should both contribute to further improving the cost effectiveness of bisphosphonates in women with post-menopausal osteoporosis.

Published evidence indicates that bisphosphonates are estimated to be similarly cost effective or cost saving in most treatment scenarios of post-menopausal osteoporosis in Switzerland and in neighbouring European countries.

Key points for decision makers

- The economic burden associated with post-menopausal osteoporosis is substantial and will continue to grow as the population ages
- Cost-effectiveness studies in Switzerland and neighbouring European countries have shown that oral bisphosphonates are, in general, cost effective and can even be cost saving relative to no treatment for fracture prevention in high-risk populations
- The main drivers of cost effectiveness in the available published studies of bisphosphonates include overall fracture risk, cost of fractures, cost of treatments, nursing home admissions and adherence to treatment
- Assuming similar clinical efficacy, lowering treatment cost (through the use of price-reduced brand-name or generic drugs) and/or improving adherence with new agents (such as intravenous bisphosphonates) would further improve cost effectiveness in women with post-menopausal osteoporosis

Osteoporosis is characterized by low bone mass and deterioration of bone tissue resulting in an increase in bone fragility and susceptibility to fracture. This progression is accelerated in women as they pass through menopause and levels of endogenous estrogen decline. Bone fractures are a costly clinical consequence of osteoporosis, with fractures of the hip, spine and the distal forearm being the most frequent type of osteoporotic fracture.[1] The clinical and economic burden imposed by osteoporosis is substantial and, due to ageing of the population, it is expected to increase rapidly in the developed world. Switzerland ranks as one of the countries with the greatest number of elderly in the resident population, and hence is faced with an increasing burden of age-related diseases.[2] The direct medical cost attributed to the hospitalization of patients with osteoporosis and/or related fractures was Swiss franc (CHF)357 million in 2000.[3] Based on a modelling study for the Swiss population, it has been projected that the proportion of residents aged ≥50 years will rise from 33.3% in 2000 to 41.3% in 2020.[4] The accompanying rise in number of osteoporotic fractures is expected to increase annual osteoporosis-related first-year fracture costs to approximately CHF518 million and population-level osteoporosis-related direct

medical costs to CHF946 million by 2020.[4] Despite publication of these projections and increased awareness of the burden imposed by osteoporosis, a nationwide survey of 3667 patients between 2004 and 2006 reported that only 24% of women and 14% of men aged ≥50 years presenting with a fragility fracture were adequately treated with a bone active intervention after the event.[5] The evidence indicates that osteoporosis remains widely under-diagnosed and under-treated in Switzerland.

Bisphosphonates act by reducing bone turnover. Treatment of osteoporosis patients with bisphosphonates has the potential to reduce the incidence of vertebral and hip fractures by approximately 50%.[6-8] Recent surveys suggest that bisphosphonates are the most commonly prescribed osteoporosis treatment in Switzerland, with alendronate, ibandronate, risedronate and zoledronic acid currently available to prescribers.[5] Although published reviews suggest that efficacy is consistent across the bisphosphonate class (when taken according to recommendations), no head-to-head trials have been performed and agents vary in terms of tolerability and route of administration, and with respect to pharmacy cost.[8-10] Orally administered bisphosphonate treatments tend to be poorly absorbed, and recent reviews of fracture endpoint trials have highlighted the association between poor patient adherence and the complex dietary and postural requirements when taking oral bisphosphonate medications.[6] The adverse effect profile of individual bisphosphonates may also play an important role in adherence. Intravenously administered bisphosphonates, either administered as 3-monthly injections or annual infusions, have the potential to improve efficacy via improved adherence to treatment.[11] With this in mind, adherence is likely to play an important part of any future cost-effectiveness evaluation of oral versus intravenous bisphosphonates (as it influences both costs and effectiveness).[12] With calls for improved patient management in Switzerland and an increasing number of patients eligible for osteoporotic therapy, there is an urgent need to assess the cost effectiveness of osteoporosis treatment options.

Published evidence has shown that the relative cost effectiveness of osteoporosis treatments varies between countries, as a number of country-specific factors (such as the underlying risk of fracture in a given population, the costs of preventive therapy and the costs of fracture treatment) play an important role.[13-15] In a previously published structured review of economic evaluations relating to osteoporosis published prior to 2005, 42 articles were identified, of which 71% concerned either the Swedish, UK or US settings.[16] A more recent review of evaluations published between 2002 and 2005 identified 22 studies, 86% of which were set in European centres and 86% of these assessed pharmacological agents (60% bisphosphonates).[17] In the present analysis, we performed a structured review of published literature relating to the cost effectiveness of bisphosphonates in the treatment of post-menopausal osteoporosis in the Swiss setting. The aim was to summarize the published evidence in the Swiss setting and identify the key factors that influence cost effectiveness by comparison with analyses from other European countries.

1. Methods

A literature search strategy was designed to identify published data on the cost effectiveness of osteoporosis treatment with bisphosphonates in post-menopausal women. The following databases were searched: MEDLINE, EMBASE, The Cochrane Library of Databases (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, the Health Technology Assessment Database and the NHS Economic Evaluation Database) and EconLit. Database searches were performed on 16 December 2009 and were defined using the medical subject headings (MeSH) terms 'bone density' OR 'fractures, bone' OR 'osteoporosis' OR 'bone demineralization, pathologic' OR 'densitometry' AND 'costs and cost analysis' AND 'humans'. Searches were limited to the last 10 years and publications in the German or English language. Editorials, letters and comment articles were excluded.

Published records identified by the literature search were screened for relevance according to the procedure outlined below, and data extraction was performed by one investigator (W. Valentine). A total of 1162 and 1663 abstracts were identified in MEDLINE and EMBASE respectively, 457 in the Cochrane library and nine in EconLit. After removal of duplicates, all articles were screened by title and abstract to identify Switzerland-specific publications on the cost effectiveness of bisphosphonate treatment of postmenopausal osteoporosis. Hand searches of relevant journals and references contained within review articles were performed to complement the findings of the database literature search.

To investigate how key parameters identified in the published studies might influence cost effectiveness in the future, European cost-effectiveness analyses captured in the systematic search of literature databases were reviewed. Studies were included if they were (i) published in 2005 or later; (ii) reported cost effectiveness of bisphosphonate versus no treatment (i.e. were analogous to the Swiss studies); and (iii) were in a comparable European setting (Austria, Belgium, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden or the UK). Although the systematic literature search also identified cost-effectiveness studies relating to the use of bisphosphonates in other patient groups (e.g. including those with cancer or inflammatory bowel disease), as well as studies relating to the use of non-bisphosphonate treatments in osteoporosis, or those based on indirect comparisons of bisphosphonates, they were excluded for the purposes of the present analysis. Reported costs were converted to CHF based on country-specific purchasing power parities for GDP[18] for the reported cost year. Where costs were reported in €, but this did not correspond to national currency, purchasing power parity GDP rates for the € zone were assumed to apply. An exception to this was the costs for Switzerland reported in € by Wasserfallen et al.,[19] which were converted back into CHF by applying the exchange rate cited in the publication of €1 = CHF1.6.

To ensure consistent use of terminology, for the purposes of the review we adopted the following recommended definitions from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR): *persistence* was defined as the length of time from initiation to discontinuation of therapy, and *compliance* was defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a regimen. *Adherence* implies both persistence and compliance.[20]

2. Results

2.1 Literature Review Results

The systematic literature search identified six articles that evaluated the costs and/or cost effectiveness of the treatment of post-menopausal osteoporosis with bisphosphonates in Switzerland, of which only two[19,21] considered cost effectiveness (table I). One reported the cost utility of treatment for osteoporosis with oral risedronate,[19] and the second described a cost-utility analysis on a screen-and-treat approach with oral alendronate.[21] A third article,[22] identified during the hand search, described an update of the previously published screen-and-treat analysis[21] with new treatment costs (table I). All of these analyses were from a healthcare payer perspective. The small number of cost-effectiveness publications specific for the Swiss setting precluded any extensive within-country comparisons between cost-effectiveness studies. We, therefore, compared outcomes with similar analyses conducted in Germany, the UK and other Western European settings based on the assumption that patient characteristics and patient management were likely to be closer to the Swiss setting than those in other parts of Europe or the rest of the world.[8,21-32]

2.2 Cost Effectiveness of Bisphosphonate vs No Treatment in Switzerland

Two analyses estimated the cost utility of a population-based screen-and-treat approach (i.e. combined dual-energy x-ray densitometry [DXA] screening of bone mineral density [BMD] and treatment with an oral bisphosphonate [alendronate]) versus a non-intervention strategy in Switzerland (table I).[21,22] A Markov model was

Table I. Comparison of estimated costs (Swiss francs [CHF]) and outcomes in cost-utility analyses in Switzerland for oral bisphosphonate use vs no treatment in elderly post-menopausal women with osteoporosis (T-score of –2.5 or less) and/or prior fracture history. Studies were conducted from a healthcare payer perspective

Study (y of value)	Treatment	Key assumptions						IC per QALY gained
		acute cost per fracture		annual cost per pt			assumed persistence rate (% of pts)	
		hip fracture	vertebral fracture	bisphosphonate	BMD testing	physician visits		
Screen and treat[a]								
Schwenkglenks and Lippuner[21] (2000)	Screening plus alendronate vs no treatment	17 557	18 162	736	300[b]	[b]	45	65 y: 70 995 75 y: 35 412 85 y: 28 170
							100	65 y: 55 729 75 y: 24 170 85 y: 19 433
Lippuner et al.[22] (2008)	Screening plus alendronate vs no treatment	17 557	18 162	485	300[b]	[b]	45	65 y: 51 997 75 y: 20 165 85 y: 6401
							100	65 y: 37 017 75 y: 9071 85 y: cost saving
Treatment only[c]								
Wasserfallen et al.[19] (2005)	Risedronate vs no treatment	24 566	21 574	761	97	82	50	Cost saving

a Based on screening women at age 65, 75 or 85 y, then treating those with osteoporosis or osteopenia in the presence of fracture.

b The BMD testing cost included medical consultation costs.

c Based on a woman aged 70 y with osteoporosis and prior fracture.

BMD = bone mineral density; **IC** = incremental cost; **pt** = patient.

used to project outcomes over patient lifetimes.[21,22] In the original report by Schwenkglenks and Lippuner[21] (and in the subsequent update[22]), women and men entered the model aged 50 years, with screening performed at a predefined age (65, 75 or 85 years) or prior to the main screening age if a fracture occurred earlier. Those patients who were identified as having osteoporosis (T-score of –2.5 or less) or osteopenia in the presence of fracture received treatment with the oral bisphosphonate. Patients with a history of fracture were at an increased risk for subsequent fractures, and the impact of alendronate was modelled using a relative risk (RR) reduction of 0.5 based on consideration of randomized controlled trials (RCTs) and a published meta-analysis.[8] It was assumed that each screening episode cost CHF300 (DXA scan plus medical consultation), and treatment costs (table I) were taken from published sources. Persistence with alendronate was assumed to either remain at 100% throughout, or to decline linearly from 100% to 65% in year 1 and from 65% to 45% between the end of year 1 and the end of the intended duration of use (realistic persistence). After discontinuation of alendronate, no further drug costs were accrued, and a linear decline in the effect of alendronate to zero was assumed over a period equivalent to the treatment period (maximum 5 years). In this way, the authors aimed to model realistic persistence with alendronate in the target population. The analysis did not account for compliance.

The screen-and-treat strategy was described by the authors as being cost effective relative to no treatment in women aged ≥75 years, as the incremental cost per QALY gained was below the assumed cost-effectiveness threshold of CHF50 000 (table I).[21] However, the screen-and-treat strategy was not considered to be cost effective in women

at the screening age of 65 years or in men at any of the screening ages. Assuming realistic persistence with treatment, the corresponding incremental costs per QALY gained for the screen-and-treat strategy in women aged 65, 75 and 85 years were CHF70 995, CHF35 412 and CHF28 170, respectively.[21] If perfect persistence (no discontinuation of treatment) was assumed, then cost effectiveness was considerably better than with the realistic scenario where persistence was modelled to decline to 45% after 5 years (table I).[21] In sensitivity analysis for the scenario assuming 'realistic persistence', outcomes were shown to be most sensitive to the cost of alendronate, duration of the alendronate effect after the end of drug administration (offset period), and the RR reduction with treatment. In contrast, the probability of a new nursing home admission after hip fracture and the cost of outpatient fracture treatment were less influential on outcomes.

In the base case, the price of alendronate was CHF61.36 per month (CHF736 per year), and decreasing the price by 30% (to CHF515 per year) resulted in an incremental cost per QALY gained of CHF22 002 in women aged 75 years, an outcome that the authors propose as being potentially relevant to the use of less costly generic alendronate in Switzerland.[21] Subsequent to the publication of this study, a price reduction by 36% for original alendronate preparations in Switzerland was announced, and the authors published revised outcomes based on the new price of CHF40.43 per month (CHF485 per year) [table I].[22] As a result of the reduction in pharmacy cost, the incremental cost per QALY gained decreased by 34% and 64% when patients were screened at the ages of 65 and 75 years, respectively, whilst the screen-and-treat strategy was cost saving at 85 years. Current (2011) prices for generic versions of alendronate are as much as 40% lower than the revised cost of original preparation alendronate (e.g. annual per-patient costs for generic Alendronat Helvepharm 70 mg are CHF287 based on listed prices obtained from the Swiss drug compendium).[33] Assuming equivalent efficacy, this would be expected to further improve the cost effectiveness of a screen-and-treat approach for osteoporosis in Switzerland.

In a third Swiss study (table I), Wasserfallen et al.[19] reported the cost utility of treatment with oral risedronate relative to no treatment over patient lifetimes, based on the use of a Markov model populated with Swiss mortality, fracture incidence and cost data from 2005. In the base-case analysis, outcomes were projected for women aged 70 years with a previous vertebral fracture and a BMD T-score of –2.5 or less. The effect of treatment with risedronate was captured in the model using RR multipliers, such that risedronate reduced the risk of hip fracture by 43%, vertebral fracture by 37% and wrist fracture by 22%. Treatment effects were based on a previously published meta-analysis of randomized trials of risedronate administered over a period of 5 years.[34] The residual effect of treatment (after 5 years of full effect) was set to 2 years in the base case, and declined linearly from 100% to 0% during this offset time.[19] Persistence was accounted for (50% over 3 years), and those patients discontinuing treatment in the first 3 months received no clinical benefit, but accrued costs. Non-compliance with treatment was not mentioned by the authors and, therefore, it is likely that, in this analysis, all patients were considered to be 100% compliant if receiving treatment and gaining the full benefit of therapy.

Over the lifetime of a 70-year-old patient in the base case, treatment with the oral bisphosphonate was dominant to no treatment (table I), as risedronate treatment was less costly (decrease of CHF1155 per patient) and more effective (increase of 0.038 QALYs).[19] Analyses conducted for different age groups demonstrated that cost effectiveness improved with increasing age. Outcomes were also investigated for multivariate scenarios defined according to age group, fracture risk factors (previous vertebral fracture, maternal history of hip fracture or history of any fracture since the age of 50 years), and residual effect after stopping therapy (either no residual effect or 2- or 5-year residual effect). Of the risk factors considered, presence of a previous vertebral fracture had the greatest impact on the incremental cost per QALY gained. In women with a prior fracture of the vertebrae alone or with a history of additional fractures, incremental costs per QALY

gained with risedronate versus no treatment were less than CHF32 000 and, in some cases, risedronate was cost saving. Sensitivity analysis showed that cost of fracture treatment, pharmacy costs and persistence assumptions were key drivers of cost effectiveness.[19]

These cost-effectiveness analyses[19,21,22] suggest that treatment of osteoporosis with a bisphosphonate is likely to be cost effective or even cost saving relative to no treatment in the Swiss setting in individuals at greatest risk of fracture. In post-menopausal women with prior fragility fracture and a T-score of −2.5 or less, bisphosphonate treatment was estimated to be cost saving and remained cost effective after changes of 50% in the cost of treatment or the cost of fractures (see section 2.4.2).[19] Outcomes were most sensitive to changes in the cost of fractures, cost of treatment, incidence and risk of fractures, and persistence with treatment.

2.3 Comparison with Other European Cost-Effectiveness Studies

Direct comparison of cost-effectiveness analyses between countries is challenging. Many aspects of country-specific analyses (e.g. study populations, competing mortality risk, assessment of fracture risk, comparators, treatment modalities and fracture costs, and quality-of-life data, to name but a few) mean that the heterogeneity between different cost-effectiveness analyses makes any meaningful comparison of results across borders difficult. In addition, costs were converted to CHF from other published currencies using purchasing power parities for GDP, which may not, due to time- and healthcare-specific fluctuations, accurately reflect current purchasing power for healthcare payers. Although the published results summarized in table II indicate that bisphosphonates are likely to be cost effective (or even cost saving) from a healthcare payer perspective in most of the scenarios investigated, the purpose of identifying these analyses was to identify the key drivers (in terms of both clinical and cost parameters) that directly influence outcomes in the published analyses. In so doing, it was hoped that the key factors likely to influence cost effectiveness in Switzerland could be identified, and the factors that should influence healthcare decision making in this area could be better understood. These factors are summarized in the following sections.

2.4 Approaches to Enhancing Cost Effectiveness in the Swiss Setting

The published studies described in this article indicate that the cost effectiveness of bisphosphonate treatment can be influenced by changes in a number of different parameters. In the context of published European cost-effectiveness analyses from the last 5 years, the following sections summarize the influence of key parameters on cost effectiveness, with particular emphasis on those that may be readily modified to improve cost effectiveness in the Swiss setting.

2.4.1 Fracture Risk and Incidence

Reduced effectiveness of bisphosphonate treatment (in terms of fracture risk) would negatively influence cost effectiveness, and it follows that the development of newer treatments with improved efficacy would improve cost effectiveness in the Swiss setting. For currently available bisphosphonates, the lack of head-to-head RCTs and between-trial heterogeneity has made efficacy comparisons difficult. However, oral bisphosphonates have been shown to significantly reduce the risk of vertebral fracture by 41–62%, and they are generally considered to be of equivalent efficacy.[6,7] If similar efficacy is assumed, then the choice of bisphosphonate would not influence fracture risk and, therefore, between-treatment differences in cost effectiveness would solely reflect differences in other drivers. Differences in persistence with treatment alternatives could influence overall effectiveness in terms of fracture risk, resulting in changes in the relative cost effectiveness of the agents.[35]

The cost-effectiveness analyses of Schwenkglenks and Lippuner[21]and Wasserfallen et al.[19] both demonstrated a strong influence of fracture incidence on cost-effectiveness outcomes. An extensive investigation of international variation in population-level hip fracture probabilities

Table II. Comparison of estimated costs and outcomes in cost-effectiveness analyses in European countries for oral bisphosphonate use vs no treatment in elderly postmenopausal women with osteoporosis (T-score of –2.5 or less) and/or prior fracture history. All costs were converted to Swiss francs (CHF), based on purchasing power parity GDP exchange rates.[18] All studies were conducted from a healthcare payer perspective

Study (y of value)	Treatment	Country	Key assumptions						IC per QALY gained[a]
			acute cost per fracture		annual cost per pt			adjustment of compliance/ persistence rates	
			hip fracture	vertebral fracture	drug[b]	BMD testing	physician visits		
Treatment only									
Brecht et al.[24] (NR)	Risedronate vs no treatment	Germany	19541	10367	1169	NR	NR	No adjustment	76220
	Alendronate vs no treatment				1209				98084
Stevenson et al.[8] (2001)	Risedronate vs no treatment	UK	18021	1497	834	100	51	No adjustment	64582
	Alendronate vs no treatment				884				49708
	Etidronate vs no treatment				478				87305
Van Staa et al.[32] (NR)	Risedronate or alendronate vs no treatment	UK	17168	1426	752	90	48	No adjustment	21172
Jansen et al.[28] (2004)	Alendronate vs no treatment	UK	17811	1628	822	94	94	No adjustment	21826
		Netherlands	18740	1041	924	147	41		27205
Hiligsmann et al.[26] (2006)	Alendronate vs no treatment	Belgium	31141–38142 (first y)	4055 (first y)	686	88	38	Compliance: 100% Persistence: 25%	26823[c]
								Full adherence	22371
Christensen et al.[25] (2002)	Alendronate vs no treatment	Denmark	NR	4267	967	256	22	Compliance: 50%	40942
								Full adherence	26574
Borgström et al.[23] (2003)	Risedronate vs no treatment	Sweden	20796	7241	901	303	260	No adjustment	1748
		Finland	13075	2513	968	158	141		34331
		Spain	15947	4971	1291	226	120		76715
		Belgium	33609	7434	851	77	40		23820
Ström et al.[31] (2004)	Alendronate vs no treatment	Belgium	32912	7280	980	74	41	No adjustment	17740
		Denmark	44857	2341	1310	105	340		3384
		France	18130	6313	912	203	47		16122
		Germany	34307	10855	1056	94	33		20512
		Italy	35124	7769	1055	169	64		38000
		Norway	48432	1858	1011	145	183		Cost saving
		Spain	15992	3537	1218	222	176		37343
		Sweden	20964	7299	872	306	262		Cost saving
		UK	35440	5155	894	107	83		7024
Screen and treat									
Müller et al.[29] (2006)	Screening plus alendronate vs no treatment	Germany	84038 (total first y)	6381	867	42	51	Compliance: 38%	13071[d]
	Screening plus risedronate vs no treatment				836				15502[d]

Continued next page

Table II. Contd

Study (y of value)	Treatment	Country	Key assumptions		annual cost per pt			adjustment of compliance/ persistence rates	IC per QALY gained[a]
			acute cost per fracture		drug[b]	BMD testing	physician visits		
			hip fracture	vertebral fracture					
Müller et al.[30] (2006)	Screening via CRFs plus alendronate vs no treatment	Germany	84 038 (total first y)	6 381 (total first y)	867	NR	51	Compliance: 38%	41 949[d]
	CRFs plus DXA and alendronate vs no treatment								13 093[d]
Hiligsmann et al.[27,e] (2006)	Screening plus alendronate vs no treatment	Belgium	31 141–38 142 (first y)	4 055 (total first y)	579	88	49	Compliance: 70% Persistence: 18%	19 911[f]
								Full adherence	2 309[f]

a Based on a woman aged 70 y with prior fracture and T-score of –2.5 or less unless otherwise indicated.

b Drug cost for bisphosphonate.

c Corresponds to a woman aged 75 y.

d Corresponds to a woman aged 70–80 y.

e Assuming same costs for hip and vertebral fracture as published in Hiligsmann et al.[26]

f Corresponds to a woman aged 75 y without prior fracture.

BMD = bone mineral density; **CRF** = clinical risk factors; **DXA** = dual-energy x-ray densitometry; **IC** = incremental cost; **NR** = not recorded.

previously categorized countries as either very high risk, high risk, medium risk or low risk.[14] Switzerland was ranked as a high-risk country. As many factors influence the incidence of fracture in a population, it is difficult to modify this parameter. However, a recent study[36] suggested that the incidence of osteoporosis-related hip and vertebral fractures within the Swiss population might be even greater than estimated in that report, and also greater than assumed in the cost-effectiveness studies of Schwenkglenks and Lippuner,[21] Lippuner et al.[22] and Wasserfallen et al.[19] Incorporation of this higher incidence value in future cost-effectiveness studies may provide a more realistic assessment of the Swiss population, and is likely to further improve projected cost effectiveness of bisphosphonate treatment in the Swiss setting.

2.4.2 Cost of Fractures

Although substantial decreases in the length of stay for hospitalized events between 1992 and 2000 resulted in a 40% decrease in direct medical costs related to acute hospitalization for osteoporosis in Switzerland, the mean cost per event was still CHF14 616 per female patient in 2000.[3] In a sensitivity analysis, Wasserfallen et al.[19] demonstrated that decreasing the cost of fracture by 50% in the Swiss setting resulted in an incremental cost per QALY gained of CHF26 350 for risedronate versus no treatment. Therefore, if further decreases in the cost of hip and vertebral fractures were to be achieved, this would have the effect of rendering treatment cost effective as opposed to cost saving.

In the studies of Schwenkglenks and Lippuner,[21] Lippuner et al.[22] and Wasserfallen et al.,[19] the direct costs of vertebral fracture and hip fracture (table I) were substantial. These direct cost estimates for fracture events are supported by similarly high costs previously published by other groups for Switzerland.[3] The cost of hip, but not vertebral, fracture in the Swiss setting is comparable to the average direct cost of fractures reported in 2001 for the EU (CHF8227 for vertebral, CHF17 175 for hip).[37] More recent cost-related data from European cost-effectiveness analyses published since 2005 and selected for

inclusion in the current review based on their comparability with the Swiss studies (i.e. bisphosphonate treatment vs no treatment in elderly post-menopausal women with osteoporosis and/or prior fracture) are shown in table II. Although the cost for hip fracture varies depending on country setting, costs in Switzerland were in line with the upper end of these estimates. Of particular note was the relatively high cost of vertebral fracture in Switzerland (table I), as this was approximately 2- to 10-fold greater than the cost of vertebral fracture in other European settings (table II). This disparity may be explained by the fact that, in the Swiss studies, vertebral fracture costs referred to only those fractures resulting in hospitalization. This was not the case in the analyses from other European countries (where costs of non-hospitalized vertebral fractures may have been captured in the estimation).

2.4.3 Treatment Costs

As demonstrated by Wasserfallen et al.,[19] reducing the cost of bisphosphonate therapy increased treatment-associated cost savings as expected, but this had a lesser impact on outcomes than variation in the cost of fractures, even though more patients would accrue treatment costs than would experience a fracture.

In contrast to the direct cost of hospitalized fracture, the annual costs of pharmacotherapy, physician visits and BMD measurements applied for Switzerland (table I), appear to be comparable to costs in other country settings (table II). The annual per-person cost of selected bisphosphonate preparations available in Switzerland varies from a low of CHF284 for generic alendronate to CHF731 for daily risedronate (Actonel®).[33] Whilst most bisphosphonates are believed to achieve similar efficacy when taken according to recommendations, recent reports suggest that generic alendronate preparations may not be associated with the same effectiveness as branded versions in clinical practice, a finding that appears to be due to reduced compliance but may also reflect reduced efficacy or increased adverse effects, although this needs further investigation.[38-40]

2.4.4 Persistence and Compliance

In the Swiss analyses, patient persistence with bisphosphonate treatment influenced treatment-associated cost savings (table I). Although it is important to note here that osteoporosis treatment remained cost saving even after accounting for discontinuation of treatment by half of all patients initiating bisphosphonate treatment in the Swiss setting,[19] this is clearly suboptimal in both clinical and economic terms, and improved persistence and compliance may improve cost savings or cost effectiveness.

Based on our search of published literature, many of the European cost-effectiveness analyses of bisphosphonate versus no treatment failed to account for either patient persistence or compliance (table II). However, the few that did provided evidence that both compliance and persistence were important drivers of cost effectiveness.[25,27,30] Additional evidence on the importance of compliance can be found in a recent modelling study designed to assess the cost effectiveness of annual infusions of the bisphosphonate zoledronic acid relative to currently available treatments (74% receiving weekly or monthly oral bisphosphonate, 16% raloxifene and 9% strontium ranelate) in the French setting.[41] Effectiveness was taken directly from clinical trials and persistence was accounted for by assuming that non-persistent patients (40–60% for oral drugs; 20–50% for zoledronic acid) had efficacy levels similar to placebo. When it was assumed that all treatments were equally effective, but differed in terms of persistence, the cost per hip, non-vertebral and vertebral fracture avoided was CHF191, CHF120 and CHF336 less with zoledronic acid infusion than with current treatment strategies over 3 years.

Orally administered bisphosphonates that can be taken once weekly (risedronate, alendronate) or monthly (ibandronate) are associated with improved persistence and compliance with therapy relative to those that are taken daily.[42,43] Unfortunately, whilst some patients benefit from the less frequent administration, overall persistence remains low, with more than 50% of patients discontinuing treatment after 12 months.[43] For patients with post-menopausal osteoporosis and who are unable to comply with oral treatment,

formulations that can be intravenously administered have the potential to improve compliance.[11] Two intravenous bisphosphonates are currently available in Switzerland for treatment of post-menopausal osteoporosis: ibandronate, which can be intravenously injected at 3-monthly intervals; and zoledronic acid, administered annually via a minimum 15-minute intravenous infusion. Nevertheless, clinical trials with the intravenously administered bisphosphonate treatments have reported efficacy equivalent to that of oral treatments with respect to BMD gains and fracture incidence as summarized in several review articles,[11,44-48] although no head-to-head trials have been conducted.

3. Discussion

Despite the significant clinical and economic burden imposed by osteoporosis in Switzerland, a systematic search of published literature revealed that very few cost-effectiveness analyses of bisphosphonate treatment in post-menopausal women have been published. Three studies were identified in the current review and, based on modelling of outcomes from RCTs, they predicted that treatment with oral bisphosphonates was cost saving for most women aged ≥70 years with osteoporosis or at least one risk factor for fracture, and cost effective for women aged ≥65 years at current prices when used as a component of a screen-and-treat programme in the Swiss setting.

The incremental cost-effectiveness estimates summarized in table I for bisphosphonates in Switzerland are comparable, and in some cases favourable, to incremental cost-effectiveness estimates for drugs used to treat other chronic diseases in Switzerland, such as pioglitazone versus placebo after macrovascular events in diabetes (CHF60 596 per QALY gained [2005 values])[49] or raltegravir versus placebo for patients with HIV-1 (CHF42 751 per QALY gained [2007 values]).[50] Although limited in number, these studies of bisphosphonate treatment were based on realistic assessments that accounted for poor persistence with oral bisphosphonates and loss of treatment effect after discontinuation of the drug.

The relative importance of individual drivers of cost effectiveness from the Schwenkglenks and Lippuner[21] and Wasserfallen et al.[19] studies was assessed using variable dependent elasticity methodology and ranked in order of importance (i.e. the highest rank reflects the input parameter where the smallest [relative] change in input parameter drives the largest [relative] change in output and, for the lowest rank, the opposite is true) [table III]. It showed that fracture cost and fracture risk (including the effect of treatment on fracture risk) are among the key drivers of the cost effectiveness of bisphosphonate treatment in the Swiss setting. In the long term, it may be possible to reduce the overall economic burden of osteoporosis by reducing these costs or developing new treatments with greater efficacy. Of the remaining influential parameters, improving patient adherence to currently available treatment is likely to be amenable to improvement. This suggested feature of intravenous bisphosphonates was deemed to improve cost effectiveness. Based on the published evidence, there is no reason to believe that intravenous bisphosphonates would not be cost effective in Switzerland. This hypothesis is supported by recent data on the cost effectiveness of an intravenous bisphosphonate versus oral treatments in the French setting.[41] For the Swiss population aged ≥65 years, the average number of physician consultations per year was 4.6 for women and 4.0 for men in 2007.[52] Therefore, the required quarterly and yearly injections of the intravenous bisphosphonates ibandronate and zoledronic acid, respectively, seem well suited for mapping routine care.

Recent publications have provided insights into the issue of persistence and compliance with bisphosphonate treatment. Review articles, several real-world surveys of oral bisphosphonate use in routine clinical practice and retrospective database analyses have emphasized the clinical and economic burden imposed by poor compliance and persistence with osteoporosis treatment.[35,53-56] Of potential relevance to the Swiss setting, a survey of oral bisphosphonate use in Germany found that 31.3% of patients discontinued once-weekly treatment after just 3 months and, by 12 months, the proportion was 53.5%.[57]

Table III. Ranking of key drivers of cost effectiveness in published Swiss cost-effectiveness analyses based on variable dependent elasticity (VDE)[a]

Variable	VDE ranking (from 1 = most influential to 8 = least influential)			Schwenkglenks and Lippuner[21]		Wasserfallen et al.[19]		
	overall ranking (combined)	Schwenkglenks and Lippuner[21]	Wasserfallen et al.[19]	change in variable (%)	change in ICER VDE	change in variable (%)	change in cost VDE	change in QALY VDE
Effect of treatment (fracture risk)	1	1	1	+30	−1.6	+30	−4.0	+1.1
				−30	−1.6	−30	−3.9	+1.1
Fracture incidence	2	3	2	+30	−1.2	+30	−2.6	+0.6
				−30	−1.0	−30	−3.1	+0.7
Persistence	3	4	3	+25	−0.6	80	−2.0	0.6
				−25	−1.2	20	1.3	1.1
Treatment cost	4	2	6	±30	−1.3	+30	+2.9	No effect
Fracture cost	5	6	4	±30	−0.7	+30	−3.7	No effect
QOL utility decrements (with fracture)	6	7	5	+30	−0.6	+30	No effect	+1.0
				−30	−0.9	−30	No effect	+1.0
Discount rate	7	5	8	+50	−0.8	+50	+0.5	−0.2
				−50	−0.7	−50	+0.4	−0.2
Residual effect of treatment (after cessation)	8	8	7	5 y	0.7	5 y	−0.7	+0.1
				None	−0.5	None	−1.0	+0.2

a VDE is a measure of responsiveness of outcomes to changes in the value of input parameters, and equals the relative percentage change in the input parameter divided by the relative percentage change in the outcome parameter compared with corresponding values in the base case. Percentage changes in input and outcome variables were calculated from the available published data to approximate the VDE. The approach taken here was a simplified application of that previously described by Ström et al.[51] Details of the VDE analysis are available from the author on request.

ICER = incremental cost effectiveness ratio; **QOL** = quality of life.

Studies in other countries have found similarly poor adherence, and comprehensive reviews of persistence and compliance in the real-life setting have documented the relationship of this to increased rates of fragility fractures.[35,53-56] Moreover, Fardellone et al.[41] recently published evidence supporting the cost-effectiveness benefits of improved compliance associated with annual zoledronic acid injection over oral bisphosphonate treatment (see section 2.4.4).

Reducing pharmacy costs by using generic bisphosphonates also has the potential to improve cost effectiveness in the Swiss setting, assuming that clinical equivalence between generic and branded agents can be demonstrated. However, in 186 post-menopausal women receiving either generic alendronate, branded alendronate or branded risedronate in Germany, adherence was poorer and BMD improvements were smaller with the generic agents than with the branded agents.[40] In this retrospective chart review, 68% of patients remained on generic bisphosphonate after 12 months versus 84% and 94% in the branded bisphosphonate treatment groups. A greater number of gastrointestinal adverse events were reported with generic therapy than with branded agents, and significantly smaller increases of lumbar spine and total hip BMD were reported with generic alendronate than with the two branded bisphosphonate originals. The observation of poorer persistence on generic agents is supported by recent data from a 1-year observational study in >32 000 patients in Canada.[58] These studies suggest that the assumption of clinical equivalence for generic bisphosphonates compared with their branded counterparts is questionable. While such questions remain open with regard to generics, there is no doubt that price reduction of original brands (e.g. in response to the commercial pressure after the introduction of generics and as reportedly done with the original brand of alendronate in Switzerland[22]) does improve cost effectiveness.

Whether cheaper original brands with possibly lower compliance/persistence are more cost effective than more expensive brands with possibly better compliance/persistence will only be answered definitively once appropriate head-to-head direct comparative endpoint trials are performed.

The burden of osteoporosis is considerable in Switzerland, and the age-independent incidence of hospitalization for osteoporosis among women is two to three times higher than for breast cancer or heart failure, and six times higher than for diabetes.[3] As the Swiss population ages, the demand for osteoporosis treatment is expected to increase substantially and efforts to further improve the cost effectiveness of treatment should be viewed as a healthcare priority.[4] It is hoped that, in the future, RCTs and observational studies comparing treatments with different administration routes and reporting hard endpoints, including hip and vertebral fracture in patients at increased risk, will confirm the impact of persistence and compliance on effectiveness and direct medical costs in the real world. Such trials should capture the clinical benefits of different administration routes and the associated persistence and compliance profile in terms of reduced fracture risk.

However, as fracture risk (and the resultant costs associated with fractures) represents an important driver of outcomes, the methods used to estimate fracture risk are key factors in any cost-effectiveness analysis. A number of modifiable and non-modifiable risk factors (e.g. age, history of previous fracture, BMD, history of maternal fractures, etc.) are known to influence fracture risk to varying degrees, and a number of different methods are available to modellers estimating fracture risk, including FRAX® (WHO fracture risk assessment tool) scores, and more simple models based on BMD and age alone. The methods used to estimate fracture risk in future cost-effectiveness analyses in the Swiss setting, therefore, warrant careful consideration. Similarly, future computer simulation modelling studies are required to estimate the likely cost effectiveness of intravenous bisphosphonates in comparison with oral formulations in Switzerland. In an ideal situation, such analyses could incorporate real-life persistence and compliance data if available from clinical studies. Additional modelling studies to evaluate long-term cost effectiveness of generic bisphosphonates in Switzerland would be useful to decision makers, with the caveat that data on the clinical effectiveness and persistence/compliance profile of these agents were available (as the assumption of clinical equivalence is questionable).

4. Conclusions

In view of the high cost of hospitalized fractures, and the demonstrated robustness of cost-effectiveness outcomes to changes in treatment cost, patient preference, resulting in enhanced persistence and compliance, may represent an additional opportunity to improve cost effectiveness. For healthcare payers, the results of the analyses presented here suggest that oral bisphosphonates represent a cost effective (or even cost saving) treatment in the management of osteoporosis.

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