Original Article

An economic evaluation: simulation of the cost/effectiveness and cost/utility of universal prevention strategies against osteoporosis-related fractures[†]

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Abstract

A patient-level Markov decision model was used to simulate a virtual cohort of 500 000 women 40 years-old and over, in relation to osteoporosis-related hip, clinical vertebral and wrist bone fractures events. 16 different screening options of three main scenario groups were compared: i) the status quo (no specific national prevention program), ii) a universal primary prevention program iii) a universal screening and treatment program based on the 10-year absolute risk of fracture. The outcomes measured were total directs costs in perspective of public health care system, number of fractures and quality-adjusted life years.

Results show that an option consisting of a program promoting physical activity and treatment if a fracture occurs is the most C/E (cost/fracture averted) alternative and also the only cost saving one especially for women 40 to 64 years old. In women who are 65 years and over, BMD based screening and treatment based on the 10-year absolute fracture risk calculated using Canadian association of radiologists and Osteoporosis Canada (CAROC) tool is the best next alternative. In terms of C/U, results were similar. For women of less than 65 years old, a program promoting physical activity emerged also as cost-saving but BMD-based screening with pharmacological treatment also emerged as an interesting alternative. In conclusion, a program promoting physical activity is the most C/E and C/U option for women of 40 to 64 years. BMD screening and pharmacological treatment might be considered as a reasonable alternative for women of 65 years and over as at a healthcare capacity to pay of CAD $ 50000 for additional fracture averted or for one QALY gained its probabilities of cost/effectiveness compared to the program promoting physical activity are 63% and 75% respectively which could be considered socially acceptable. Consideration of the indirect costs could change these findings.

Key words: osteoporosis, screening, computer simulations, cost/effectiveness, cost/utility, prevention, bone fractures.

Introduction

Osteoporosis is a disease characterized by deterioration in the micro-architecture of bone tissue that leads to increased bone frailty and susceptibility to fragility fractures. In Canada and most Western countries, its prevalence in the population of postmenopausal women 50-54 years-old is about 4.0%. This increases to 45% in women 85-89 years-old[1]. In women over 50 years old, bone loss leads to a lifetime risk of fractures of approximately 40%[2-3]. It has been estimated that two osteoporosis-related fractures occur every hour in women 50 years and older in Canada [3].

Several interventions have been shown to be effective to prevent osteoporosis-related fractures. Primary prevention consists of interventions such as promotion of calcium and vitamin D supplements and of physical activity [1, 4-6]. Screening aims at the identification of women at high risk followed by initiation of pharmacological therapy [7]. Recently published 2010-osteoporosis best practice guidelines propose an integrated approach to osteoporosis management guided by an assessment of the patient's 10-year absolute risk of bone fractures[4]. Pharmacological treatment is recommended for women who have at least 20% ten-year basal absolute risk [4]. Yet, in this framework, different intervention options exist.

To our knowledge, no Canadian study has compared the cost/effectiveness and cost/utility of those different options. Using a patient-level Markov model, we compared the expected cost/effectiveness (C/E) and cost/utility (C/U) of 16 different interventions that covered three main scenario groups namely: 1- no national prevention program, which is the present situation in our jurisdiction. 2- a universal primary prevention program and 3- a universal risk of fracture screening program.

Methodology

Modeling and input parameters

A patient-level Markov model (SPLMM) using an individual sampling approach[8-9] was used to simulate each of the 16 possible scenarios to compare (see above) (Figure1).The three most prevalent fracture sites were considered: hip, clinical vertebral and wrist [10-14]. The maximum number of hip fractures in a single individual was considered to be two in a lifetime as we assumed that all hip fractures lead to hemiarthroplasty. As we considered age-specific annual probability of fracture by type of fracture and BMD, the state-transition model was divided into one-year cycles.

Insert Figure 1

A virtual population of 500 000 women 40 years old and older was generated. This population had the age distribution of a typical industrialized country population[15]. The population was followed with one-year cycles until all individuals have died. Detailed input parameters are presented in Table 1. Baseline parameters were retrieved from peer-reviewed published studies prioritized according to the following order: Quebec, other Provinces of Canada, USA, Europe and Australia. A systematic search of the peer-reviewed literature, guidelines and government reports was performed to define the range of values to be used for sensitivity analyses. Outcomes considered were the total number of fractures (wrist, hip and clinical vertebral) for

the entire population, as well as direct costs for the public health care system and QALYs. Simulations were performed with two types of cohorts: 1) a single cohort of women 40 years old and over followed until their death. 2) the previous cohort to which were added annually a new cohort of 40 years-old women over the first 10 years of the simulation, as performed in a previous work[16], and also followed until their death.

The population was categorized in age groups of 5 years intervals (40-44; 45-49, etc.). However, the analyses showed that only a distinction between less than 65 years old and 65 and over brought age-related specific results. Only the results for these later groups are presented here.

Options and scenarios

Table 2 presents the 16 options related to the 3 scenario groups that were compared.

The *first scenario*, termed "status quo", does not correspond to an absence of primary or secondary prevention, but to the absence of a specific national program to initiate preventive activities in women. In other words, this scenario considers the proportion of women who presently undertake preventive activities. Following a fracture, a woman may be investigated or not for osteoporosis[19]. Depending on the investigation outcome, she has a certain probability of being treated with pharmacotherapy (risedronate) or of being proposed to take calcium and vitamin D[19, 44]. In the baseline scenarios, risendronate is to be taken until death. However, in sensitivity analyses, we considered 5 years and 10 years duration of pharmacotherapy. The compliance rate to osteoporosis treatments in Canada was taken into account[20].

The model considers the risk of death following a fracture[21] and the proportion of women with a fracture who get enrolled into a physical rehabilitation program[22]. It considers the specific effects of biphosphonate (risedronate), vitamin D + calcium and physical activity on the risk of hip, wrist and clinical vertebral fractures by BMD and age category[5, 27]. It also takes into account the probability for a woman with a wrist fracture to undergo surgery[25], with a hip fracture to be transferred to long term care[22-24] and ambulatory rehabilitation[22], and with a clinical vertebral fracture to be hospitalized[22].

The *second scenario* refers to primary prevention of osteoporosis. We tested the options recommended by the 2010 Canadian guidelines on diagnosis and management of osteoporosis: 1) supplements of calcium and vitamin D; 2) promotion of physical activity (which can be simply walking every day); and 3) a combination of physical activity and calcium and vitamin D[4]. The options were applied to the age-weighted proportion of

women who, in the province of Quebec, do not practice some kind of physical activity according the definition of Statistics Canada[18, 45-46], or do not take vitamin D and calcium supplements[18, 46]. The baseline proportion of these women who adopt a preventive option was inferred from the participation rate in the Quebec national screening program for breast cancer[31]. For the options that combine physical activity and supplementation of vitamin D and calcium, the simulation considered the highest effect of any of them on fracture risks reduction. When a fragility fracture occurred, the progression in the model was similar to the one described in the first scenario.

The *third scenario* refers to a universal screening program, that would aim at identifying women at risk of having an osteoporosis-related fracture, using the Canadian Association of Radiologists and Osteoporosis Canada's screening tool (CAROC), which is based on age, gender, bone mineral density, prior fracture and prior use of glucocorticoids [17]. This option complies with the 2010 Canadian guidelines on diagnosis and management of osteoporosis[4] recommended by the Canadian Task Force on Preventive Health Care[1] and the Canadian Consensus Conference on the Osteoporosis 2006[47]. The possibility for a pre-screening step before considering women for BMD screening was also included in the simulation. The three questionnaires considered are those with the highest sensitivity/specificity related to being osteoporotic and/or that are validated for the Canadian population, namely: the Simple Calculated Osteoporosis Risk Estimation (SCORE)[29]; the Osteoporosis Risk Assessment Instrument (ORAI)[30] and the Osteoporosis Self-assessment Tool (OST)[28]. Baseline participation rate for the screening scenario was estimated to be the same as for primary prevention. The model took into account the tests' sensitivity and specificity. According to the pre-screening and CAROC screening results, women are categorized into three groups: low risk (< 10% ten-year risk of fracture), moderate risk (between 10% and 20% ten-year risk of fracture) and high risk (> 20% ten-year risk of fracture) based on thresholds defined by the

Canadian association of Radiologists and Osteoporosis Canada[17]. Low risk patients receive a recommendation to adopt one of the preventive options (physical activity and/or vitamin D and calcium). A moderate risk implies preventive options or pharmacotherapy (risedronate) when other risk factors are present. A high risk implies pharmacologic treatment (risedronate). When a fragility fracture occurs, the progression in the model proceeds as described in the first scenario. The model considers that preventive or curative treatments are undertaken without interruption until death occurs[4].

Utilities

The Health Utilities Index III (HUI3) was used to score the utility of different health states that occurred in the model over time. These calculated utility scores were validated by an expert committee and were used in the base case scenarios.. Published utilities as described in the literature [32] [33] [34] were used in sensitivity analyses (Table 1).

Costs

In Canada, all services considered as medically required (except ambulatory prescribed drugs) are generally provided exclusively within the public healthcare system and are free of charge. The Quebec Ministry of Health and the Public Medical Insurance perspectives were therefore considered. Only direct costs were estimated.

Cost items included fracture-related health care and rehabilitation services, long-term hospitalization for people with loss of autonomy following a fracture, prevention campaigns, primary screening for osteoporosis, drug prophylaxis and treatment of osteoporosis, medical follow-up of patients with and without osteoporotic fracture. Cost of ambulatory-provided drugs was attributed to the public health care system and not distributed between patients and public insurers because of the complexity of coverage eligibility in the province.

The fiscal year 2007-2008 was used to calculate unit prices presented in Table 6. Unit prices for services obtained in the public health care were provincial averages calculated from the Quebec government databases (SIFO and APR-DRG). Unit prices of clinical activity centers were increased to reflect support activities centers using the direct method[48]. Costs for laboratory and imaging tests were based on the technical units in the province of Quebec [36]. The average cost of national campaigns of prevention in Quebec (CAD $3-5 per capita) was used as the cost for a physical activity promotion campaign [42]. Public health insurance fees paid to general practitioners and specialists were considered[35]. For pharmaceuticals, the cheapest in the list of drugs covered by the public health insurance was used (e.g. Risendronate as the biphosphanate), to which was added a 6% for wholesalers and the pharmacist's prescribing fee paid by the public insurance. The average per diem calculated by the Ministry of Health and Social Services was used for long term hospitalization[39] All costs and outcomes were discounted at a rate of 3%, and sensitivity analyses were performed with values of 0% and 5%.

Simulations

In order to produce a distribution curve, simulations for each option were repeated 1000 times, each time on a newly generated (i.e. different) virtual population. Simulations were performed with *SCHNAPS[8-9]*, a simulator running on the *COLOSSE* supercomputer of the CLUMEQ consortium (www.clumeq.ca).

Sensitivity analyses

One way sensitivity analyses were performed using the variables considered most influent on the outcomes in order to evaluate the eventual impact of each single parameter on the results. We tested the minimum and the maximum value for each of these variables (Table 1). Subsequently, multi-way probabilistic sensitivity analyses were performed. Simulation for each option was also repeated 1000 times to ensure the stability of results. A cost

effectiveness and a cost-utility acceptability curve were produced in order to better define the uncertainty of the ICERs of the best alternatives[49] .

Model validation

The model and simulation data were validated by three osteoporosis experts. Data produced were validated by comparison with expected data (such as the number of fractures, mortality rates per age, costs and effectiveness of interventions)[14]. A less than 5% difference with expected results based on the literature was sought. For example, our model estimated the proportion of 40-year-old women who would have a fracture during their remaining lifetime to be 17.9% for hip fractures and 16.07% for wrist fractures, and 15.83% for clinical vertebral which were similar to published estimates [2, 13-14].

Ethics Committee

This project was approved by the Research Ethic Committee of Laval University. None of the authors felt that he/she was in conflict of interest while participating to this study.

Results

Results are presented for women of 40 to 64 years old and for women of 65 years old and over at the start of the simulation. Results for other categories (40-49, 50-59, 60-69, 70-79, and 80 and +) are available upon request.

The most effective option for reducing the total number of fractures appeared to be a universal BMD testing program followed by the estimation of the 10-year absolute fracture risk with the CAROC-tool, and the treatment of women at high risk for osteoporosis-related fractures and the promotion of physical activity as well as the intake of vitamin D and calcium among non-high risk women, emerged as.

However, in terms of cost-effectiveness (Tables 3.1 and 3.2), for women 40 to 64 years old at the beginning of the simulation, a program promoting physical activity for sedentary women emerged as the most interesting option. It is effective and cost-saving. Compared to the *status*

quo, it is dominant. Scenarios based on screening for women at risk for fracture, then treating those considered at high risk and promoting preventive activities for the others are effective but their ICERs compared to the cheapest alternative are all larger than CAD $ 100 000/fracture averted.

However, in women 65 years old and over, a BMD screening program followed by estimation of the 10-year absolute risk of fracture using the CAROC tool and pharmacological treatment for women considered at high risk for fractures, while promoting of preventive activities for others could be considered as a reasonable alternative, as its ICER compared to a program aiming at increasing physical activity among women, is less than CAD$ 65000 per fracture avoided.

From a cost/utility perspective, results are similar (Tables 4.1 and 4.2). For women who younger than 65 years old, a program to incite sedentary women to undertake physical activities emerged also as the less costly, the more effective and the one with the most interesting C/U ratio. A BMD screening program with estimation of the 10-year absolute risk of fracture using the CAROC tool and pharmacological treatment for women considered at high risk for fractures, as well as the promotion of preventive activities for others also emerges as a possible alternative as its ICER compared to a program promoting physical activity is about 50 000/ per QALY gained.

The addition of new cohorts of 40 years old women for the first 10 years of the simulation did not influence the ranking of the most desirable options and even improved their overall cost/utility and cost/effectiveness (data not shown).

Sensitivity analyses

Cost/effectiveness and cost/utility results were robust to sensitivity analyses: the ranking of the most promising scenarios remained unchanged. However, we observed that a change of certain parameters did have a sensible impact on cost/effectiveness of interventions when compared to the base case scenario. For example, with a stronger participation rate to prevention or screening strategies, the ICER of CAROC+ vitamin D and calcium + physical activity was improved, i.e. 17% lower. The same options improved by 25% in the case of a higher efficacy of risendronate. In contrast, lower effects of vitamin D and calcium as well as physical activity, a higher discount rate (5%), a lower participation rate increased the ICERs compared to the base case scenario but did not change the ranking of the most promising options. In multi-ways sensitivity analyses, results were also robust. The rank order of the strategies did not change and the ICER for each strategy remained relatively stable (data not shown).

When cost/effectiveness and a cost/utility acceptability curves were produced for women 65 years old and more to compare the program promoting physical activity with a BMD screening program with the supplementation of vitamin D, calcium and promotion of physical activity suggested to women at low and middle risk, it appeared that at a ceiling ratio of CAD$ 50 000 generally suggested as a threshold to adopt an intervention [50], there is respectively a probability of 63% and of 75% that the screening program is cost/effective (Figure 2 and Figure3).

Insert figure 2 and figure3

Discussion

This paper presents data on cost/effectiveness and cost/utility of 16 different options for the prevention of osteoporosis-related fractures including those proposed by the recent 2010 Canadian guidelines on diagnosis and management of osteoporosis. To our knowledge, our study is the first modeling approach that compared prevention, screening and the use of the CAROC tool for the identification of women who should benefit from a pharmacological or a preventive intervention. Other modeling approaches have generally used the BMD T-score as a criterion for pharmacological treatment.

In terms of effectiveness (fractures averted), the preferred option was BMD screening for women for osteoporosis-related fracture and the determination of their 10-year absolute risk with the CAROC tool, followed by a pharmacologic treatment for those at risk and a non-pharmacologic preventive intervention (physical activity plus vitamin D and calcium) for those at moderate and low risk. However, due to its lower costs, the promotion of physical activity (followed by treatment when a fracture occurs) is the most C/E option for women between 40 and 64 years old. Indeed, because all options have a modest effect on reducing the number of fractures in the general population compared to the changes in costs, effectiveness does not significantly influence C/E ratios. This is particularly obvious for women younger than 65 years old at the beginning of the simulation and could be due to the fact that the prevalence of osteoporosis and osteoporosis related-fractures is lower in this group. For older women at the beginning of the simulation, a BMD screening program might be considered as the best C/E option. Its ICER compared to the promotion of physical activity is in the order of CAD $ 60 000 per fracture averted and CAD $ 50 000 per QALY gained. The probabilistic sensitivity analyses showed that at CAD $ 50 000/additional fracture averted, the probability that this option is cost/effective is of 63%. At CAD $ 50 000/QALY gained, it is 75 %. A

ceiling ratio of $ 50 000 is generally suggested as a threshold to adopt an intervention in North America[50] One notes that a BMD screening program for 65 years old and over women is coherent with the Canadian [4] and NOF[51] guidelines.

Ranking of the various options tested by C/U and C/E appeared similar. However, differences in QALYS were marginal, and might be explained by the fact that life expectancy differs very little from one option to another, and that the impact of events on utilities of a few individuals inside the virtual population does not much influence the average utility of the entire population. Similar results were reported in other simulations[52-53].

This research has also some limitations. The main limitations of such a study are related to the mapping of the complex reality. Indeed, some degree of simplification was needed [54-55] For example, our model considered only three sites of osteoporosis-related fracture (hip, clinical vertebral and wrist), in spite of the fact that osteoporosis-related fractures might affect other sites such as the proximal humerus, the pelvis, etc. Taking these other sites into account could increase the costs of strategies and affect the C/E and/ or C/U ratios. In addition to that, we did not take into account non-clinical vertebral fractures as we considered that they do not often retain medical attention, thus do not impact costs very much. We acknowledge that these fractures may cause some disutility to patients that might affects QALYs results.

Another limitation to the present study relates to the rate of participation in interventions to prevent osteoporosis-related fractures. We used the same participation rate as the rate of the Quebec public breast cancer screening program. Yet, reality might be slightly different because osteoporosis and breast cancer are different problems. We considered the Quebec breast cancer screening program participation rate because it is the only universal screening program in our population that targets women and for which data exist. Furthermore, we assumed that the participation rates are similar for all interventions (screening and lifestyle) which may not reflect the reality as we know that, in general, the uptake rates related to

behavior changes are low when compared to screening with non-invasive tests [56-57]. Another limitation of this work is that we did not model the side effects of drug treatments or the potential additional benefits of osteoporosis prevention and treatment on other health problems (e.g. the effects of physical activity on cardiovascular problems). Also, patients were considered as compliant or not, and the model did not consider the reduced effects of poor observance. In addition, the model assumed the same adherence rate for pharmacological therapy as for lifestyle changes. This might not reflect the real world where lifestyle are difficult to change[56-57]. However, we believe that the probabilistic sensitivity analyses done have solved partially this issue. Another limit is that the model did not consider the cumulative effect of various interventions performed concomitantly, such as physical exercise and vitamin D and calcium intake. Indeed, there is no data available on the combined effect of these interventions[4]. Adopting a conservative approach, we considered the highest effect of any of them on fracture risk reduction knowing that this might not adequately reflect the reality, as a combination effect could increase the effectiveness of some interventions. Also, our analyses were limited to direct costs borne by the public healthcare perspective. The fact that we did not take account of indirect costs could provide another ranking especially for physical activity program for which indirect costs are high. For example, we did not consider investments by the government in sports facilities or individual directs costs spent by individuals to use these facilities.

Finally, one should be cautious about generalizing our results although the scenarios were chosen on the basis of reasonable practices promoted for the entire Canadian context [48, 54]. Regarding other countries, one might suppose that our results could be reproduced in other health care systems as the CAROC-based screening tool recommended in Canada, has a 90% concordance in risk assessment with the FRAX® tool preferred in other countries such as the

UK, the USA, Sweden and Switzerland[17, 19] [58]. In any case, whether these results apply to other health care jurisdictions, remains to be confirmed.

Conclusion

A program promoting physical activity is the most C/E and C/U option for women of 40 to 64 years. A BMD screening and treatment based on 10-year absolute risk of fracture calculated by CAROC tool can be considered as a reasonable alternative for women who are 65 years old or more, if an incremental cost of CAD $ 50 000/additional fracture averted with a probability of cost/effectiveness of 63%, and CAD $ 50 000/QALY gained with a probability of cost/effectiveness of 75 % are considered as socially acceptable.

Author contributions

All authors: Conception, design, acquisition and validation of data

AD, MG, NL, DR, SM, FR, CG: analysis and interpretation of results.

DR, NL, AD, MG, CL, DJ: Drafting the article

SM, FR, SJ, DR: Critically revising of the article

All authors approved the final version of article.

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Data sharing statement

Data not shown can be available upon request to corresponding author, Daniel Reinharz (Daniel.Reinharz@fmed.ulaval.ca).

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Table 1: Input parameters

Parameter	Base case	Range for sensitivity analyses	Distribution	Source
BMD related-risk of fractures (Hip, clinical vertebral and wrist)	Calculated using data from references		-	[2, 10, 14]
Ten-year absolute risk of fractures and categorization (low, moderate, high risk)	Calculated using data from references		-	[17-18]
BMD distribution	Estimated from a representative cohort of 2104 women of 40 years and older		-	[18]
Osteoporosis investigation after fracture	0.21	0.017-0.50	Uniform	[19]
Osteoporosis treatment/prevention after fracture	0.756 if osteoporosis 0.294 if low BMD 0.09 if normal BMD		-	[19]
Compliance rate to osteoporosis treatments	0.49	30-75	Uniform	[20]
RR death following hip and clinical vertebral fracture	4.31 (hip) 2.85 (vertebral) Probability of death=RRX probability of age specific death probability in Quebec		-	[15, 21]
Acute rehabilitation for hip fracture	0.48		-	[22]
Long care (hip fracture)	0.20	0.10-0.282	Uniform	[22-23] [24]
Wrist fracture surgery	0.18		-	[25]

Clinical vertebral fracture hospitalisation		0.10			-	[22]
RR fracture	Risendronate	Hip : 0.72 Clinical vertebral : 0.58 Wrist : 0.82		0.58 to 0.88 0.50 to 0.67 0.74 to 0.90	Log normal	[26]
	Vit D and calcium	0.88		0.83-0.95	Log normal	[6]
	Physical activity (hip only)	0.62		0.54-0.69	Log normal	[27]
Performance of questionnaire		Sens.	Spec.	Sens Spec		
	OST	0.768	0.514	0.70-0.95 0.30-0.70	Uniform	[28]
	SCORE	0.90	0.32	0.80-100 0.20-0.50	Uniform	[29]
	ORAI	0.933	0.464	0.85-100 0.30-0.80	Uniform	[30]
Participation rate to interventions		0.531		0.30-0.70	Uniform	[31]
Utilities			**Score calculated**	**Sensitivity analyses range**	**Distribution**	
Hip fracture	Hospitalization post fracture		0.30	0.51-0.60	Uniform	[32]
	Rehabilitation		0.56	0.63-0.70	Uniform	[32]
	Post-rehabilitation		0.85	0.73-0.90	Uniform	[32]
Clinical vertebral fracture	Hospitalization		0.33		-	

	Rehabilitation	0.68			-	
	Post-rehabilitation	0.85	0.76-0.90		Uniform	[33] [34]
Wrist fracture	Emergency room	0.61			-	
	Rehabilitation	0.88			-	
	Post-rehabilitation	1	0.82-1		Uniform	[33]
			Costs			
	Item	**Probability**	**Frequency**	**Cost (CAD $)/person**	**Distribution**	
Hip fracture	Acute care (Emergency and surgery)	1	1	4 070	-	[22, 24, 35-37]
	Hospitalization	1	14 days	19 760 ($15808 - $23712)	Uniform	[38]
	Inpatient medical visits	1	14	229	-	[35]
	Acute rehabilitation	0.48	30 days	24 639	-	[22, 24] [35] [36]
	Long term care	0.20	1 year	74 646	-	[22, 24, 39]
	Follow-up	0.80	3 medical visits, 3 control X-Rays, 7 physiotherapy sessions	990	-	[35-36] [22, 37]

Clinical vertebral fracture	Acute care (emergency visit)	1	1	1 004	-	[22, 35-36]
	Hospitalization	0.1	9 days	8047 ($6261 -$9891)	Uniform	[22]
	Inpatient medical visits	1	9	146	-	[22, 35]
	Follow up	1	2 control X-Rays, 2 control medical visits, 7 physiotherapy sessions	550	-	[22, 35-36]
Wrist fracture	Acute care + conservative treatment	0.82	1	1250	-	[22, 25, 35-36]
	Acute care + surgery	0.18	1	3839	-	[22, 25, 35-36]
	Follow-up	1	2 control X-Rays, 2 control medical visits, 7 physiotherapy sessions	467	-	[22, 35-36]
Osteoporosis screening	Medical visit and exams	1		160	-	[1, 35-36]
	DXA	1		107.5	-	[1, 4, 35-36, 40]

Osteoporosis treatment	Vit D and calcium	Annual	160	-	[4, 41]
	Physical activity	Annual	5	-	[4, 42]
	Biphosphanate (Risendronate)	Annual	162.25	-	[4, 41]
Follow-up	Follow-up medical visit	annual	99.53	-	[1, 35-36, 43]
	Control DXA	2 years or 5 years (if low risk of fracture)	98.5	-	[4, 35-36]
Discount rate			3 % (0 and 5)	-	

Table 2. Simulated options

Scenario group	Option/intervention	Description
No specific program	Status quo	Current situation where there is no specific universal primary prevention or universal screening
Universal primary prevention	Physical activity	Proposed to women who don't do currently physical activity and pharmacological treatment if a fracture occurs
	Vitamin D and calcium	Proposed to women who don't take Vitamin D and calcium currently and pharmacological treatment if a fracture occurs
	Vitamin D and calcium + Physical activity	Proposed to women who, currently, don't do physical activity and don't take Vitamin D and calcium and pharmacological treatment if a fracture occurs.
Universal screening	BMD/CAROC + Physical activity	- Universal screening by CAROC with BMD; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; -Physical activity for women who don't need pharmacological treatment.
	BMD/CAROC + Vitamin D and calcium	- Universal screening by CAROC with BMD; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; -Vitamin D and calcium for women who don't need pharmacological treatment.
	BMD/CAROC+ Vitamin D and calcium + physical activity	- Universal screening by CAROC with BMD; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Vitamin D and calcium plus physical activity for women who don't need pharmacological treatment.

	ORAI/CAROC + physical activity	- Universal prescreening by ORAI tool; - Screening by CAROC with BMD for women who are positive to ORAI; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Physical activity for women who don't need pharmacological treatment.
	ORAI/ CAROC + Vitamin D and calcium	- Universal prescreening by ORAI tool; - Screening by CAROC with BMD for women who are positive to ORAI; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Vitamin D and calcium for women who don't need pharmacological treatment.
	ORAI/ CAROC + Vitamin D and calcium + physical activity	- Universal prescreening by ORAI tool; - Screening by CAROC with BMD for women who are positive to ORAI; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Vitamin DF and calcium plus physical activity for women who don't need pharmacological treatment.
	OST /CAROC + physical activity	- Universal prescreening by OST tool; - Screening by CAROC with BMD for women who are positive to OST; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Physical activity for women who don't need pharmacological treatment.

	OST/ CAROC+ Vitamin D and calcium	- Universal prescreening by OST tool; - Screening by CAROC with BMD for women who are positive to OST; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Vitamin D and calcium for women who don't need pharmacological treatment.
	OST /CAROC + Vitamin D and calcium + physical activity	- Universal prescreening by OST tool; - Screening by CAROC with BMD for women who are positive to OST; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Vitamin D and calcium plus Physical activity for women who don't need pharmacological treatment.
	SCORE/ CAROC + physical activity	- Universal prescreening by SCORE tool; - Screening by CAROC with BMD for women who are positive to SCORE; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Physical activity for women who don't need pharmacological treatment.
	SCORE/ CAROC + Vitamin D and calcium	- Universal prescreening by SCORE tool; - Screening by CAROC with BMD for women who are positive to SCORE; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Vitamin D and calcium for women who don't need pharmacological treatment.

	SCORE/ CAROC + Vitamin D and calcium + physical activity	- Universal prescreening by SCORE tool; - Screening by CAROC with BMD for women who are positive to SCORE; - Pharmacological treatment to women with 10-year risk of fracture ≥ 20%; - Vitamin D and calcium plus Physical activity for women who don't need pharmacological treatment.

Table 3: Cost/effectiveness results
3. 1. Women of 40-64 years (n =363042)

Option	Total costs ($CAD)	Incremental costs	Total fractures	Fractures averted	ICERs
Physical activity	1 752 926 600		215 330		Baseline*
Status quo	1 755 241 287	2 314 687	219 013	-3 683	-
OST/CAROC + Physical activity	2 005 406 312	250 165 025	213 940	5 073	-
ORAI/CAROC + Physical activity	2 009 581 197	474 885	213 925	15	-
SCORE/CAROC+ Physical activity	2 011 844 082	2 262 885	213 930	-5	-
BMD/CAROC+ Physical activity	2 016 897 393	5 053 311	213 890	40	-
OST/CAROC + Vitamin D and calcium	2 085 851 423	68 954 030	213 826	64	-
OST/CAROC +Physical activity+ Vitamin D and calcium	2 096 519 944	668 521	213 824	2	-
ORAI/CAROC+ Vitamin D and calcium	2 097 619 345	1 099 401	213 825	-1	-
SCORE/CAROC + Vitamin D and calcium	2 097 676 214	56 869	213 820	5	-
BMD/CAROC + Vitamin D and calcium	2 105 354 023	7 677 809	213 834	-14	-
SCORE/CAROC + Physical activity + Vitamin D and calcium	2 107 272 843	1 918 820	211 976	1 858	105649
ORAI/CAROC + Physical activity +Vitamin D and calcium	2 107 327 214	54 371	211 990	-14	-
BMD/CAROC + Physical activity + Vitamin D and calcium	2 115 595 462	8 268 248	211 952	38	346776
Physical activity + vitamin D and calcium	214 2763 906	27 168 444	212 180	-228	-
Vitamin D and calcium	2 144 102 484	13 385 578	215 131	-2 951	-

*Less expensive strategy

[**]Dominated strategies are those that were found to be less efficacious and more expensive than another strategy (strict dominance) or to have an incremental cost-effectiveness ratio that is greater than that of the next, more effective, and more expensive alternative (extended dominance).

3.2 65 years and + (n = 136958)

Option	Total costs ($CAD)	Incremental costs	Total fractures	Fractures averted	ICERs
Physical activity	1 002 395 979		61 976		
Status quo	1 025 394 048	22 998 069	63 564	-1 588	-
CAROC + Physical activity + Vitamin D and calcium	1 071 691 507	46 297 459	60 825	2 739	60205
OST/CAROC +Physical activity+ Vitamin D and calcium	1 086 269 626	14 578 119	61 280	-455	-
SCORE/CAROC + Physical activity + Vitamin D and calcium	1 089 941 050	3 671 424	61 219	61	-
ORAI/CAROC + Physical activity +Vitamin D and calcium	1 091 247 887	1 306 837	61 210	9	-
Physical activity + vitamin D and calcium	1 092 852 516	1 604 629	61 187	23	-
OST/CAROC + Vitamin D and calcium	1 104 577 805	11 725 289	62 073	-86	-
Vitamin D and calcium	1 107 165 714	2 587 909	62 215	-142	-
SCORE/CAROC + Vitamin D and calcium	1 109 593 435	2 427 721	62 057	158	-
ORAI/CAROC+ Vitamin D and calcium	1 110 539 440	946 005	62 073	-16	-
CAROC + Vitamin D and calcium	1 111 676 305	1 136 865	61 999	74	-
OST/CAROC + Physical activity	1 121 427 790	9 751 485	62 024	-25	-
ORAI/CAROC + Physical activity	1 121 744 178	316 388	61 904	120	-
SCORE/CAROC+ Physical activity	1 121 755 853	11 675	61 922	-18	-
CAROC+ Physical activity	1 122 808 961	1 053 108	61 901	21	-

*Less expensive strategy

[**]Dominated strategies are those that were found to be less efficacious and more expensive than another strategy (strict dominance) or to have an incremental cost-effectiveness ratio that is greater than that of the next, more effective, and more expensive alternative (extended dominance).

Table 4: Cost utility results
4.1 40-64 years (n =363042)

Option	Cost/person ($CAD))	Incremental cost/ person	Qalys/person	Incremental Qalys	ICURs
Physical activity	4 828		20.7225	Baseline*	
Status quo	4 835	7	20.71274	-0.00976	-**
OST/CAROC + Physical activity	5 524	689	20.72022	0.007446	-
ORAI/CAROC + Physical activity	5 535	9	20.72273	0.00251	-
SCORE/CAROC+ Physical activity	5 542	7	20.723	0.00027	-
BMD/CAROC+ Physical activity	5 556	14	20.72282	-0.00018	-
OST/CAROC + Vitamin D and calcium	5 746	204	20.72308	0.00026	-
OST/CAROC +Physical activity+ Vitamin D and calcium	5 775	29	20.72611	0.00303	-
ORAI/CAROC+ Vitamin D and calcium	5 778	3	20.72097	-0.00514	-
SCORE/CAROC + Vitamin D and calcium	5 780	2	20.72144	-0.00047	-
BMD/CAROC + Vitamin D and calcium	5 799	19	20.72081	-0.0063	-
SCORE/CAROC + Physical activity + Vitamin D and calcium	5 804	5	20.72655	0.00574	-
ORAI/CAROC + Physical activity +Vitamin D and calcium	5 805	1	20.72584	-0.00071	-
BMD/CAROC + Physical activity + Vitamin D and calcium	5 827	22	20.72672	0.00088	239573
Physical activity + vitamin D and calcium	5 902	75	20.72576	-0.00086	-
Vitamin D and calcium	5 906	4	20,71946	-0,0064	-

* Less expensive strategy
**Dominated strategies are those that were found to be less efficacious and more expensive than another strategy (strict dominance) or to have an incremental cost-effectiveness ratio that is greater than that of the next, more effective, and more expensive alternative (extended dominance).

4.2 65 years and + (n = 136958)

Option	Cost/person ($CAD))	Incremental cost/ person	Qalys/person	Incremental Qalys	ICURs
Physical activity	7 319		11,31492		
Status quo	7 487	168	11,29549	-0,01943	
BMD/CAROC + Physical activity + Vitamin D and calcium	7 825	338	11,32407	0,02858	55 300
OST/CAROC +Physical activity+ Vitamin D and calcium	7 931	106	11,31566	-0.00841	-
SCORE/CAROC + Physical activity + Vitamin D and calcium	7 958	27	11,31702	0.00136	-
ORAI/CAROC + Physical activity +Vitamin D and calcium	7 967	9	11,31813	0.00111	-
Physical activity + vitamin D and calcium	7 979	12	11,3193	0.00117	-
OST/CAROC + Vitamin D and calcium	8 065	86	11,30823	-0.01107	-
Vitamin D and calcium	8 084	19	11,30893	0.0.0007	-
SCORE/CAROC + Vitamin D and calcium	8 102	18	11,30711	-0.00182	-
ORAI/CAROC+ Vitamin D and calcium	8 108	6	11,31093	0.00382	-
BMD/CAROC + Vitamin D and calcium	8 117	9	11,30714	-0.00379	-
OST/CAROC + Physical activity	8 188	71	11,31116	0.00402	-
ORAI/CAROC + Physical activity	8 190	2	11,31085	-0.00031	-
SCORE/CAROC+ Physical activity	8 191	1	11,31238	0.00153	-
BMD/CAROC+ Physical activity	8 198	7	11,31195	-0.00043	-

*Less expensive strategy **Dominated strategies are those that were found to be less efficacious and more expensive than another strategy (strict dominance) or to have an incremental cost-effectiveness ratio that is greater than that of the next, more effective, and more expensive alternative (extended dominance).

List of figures

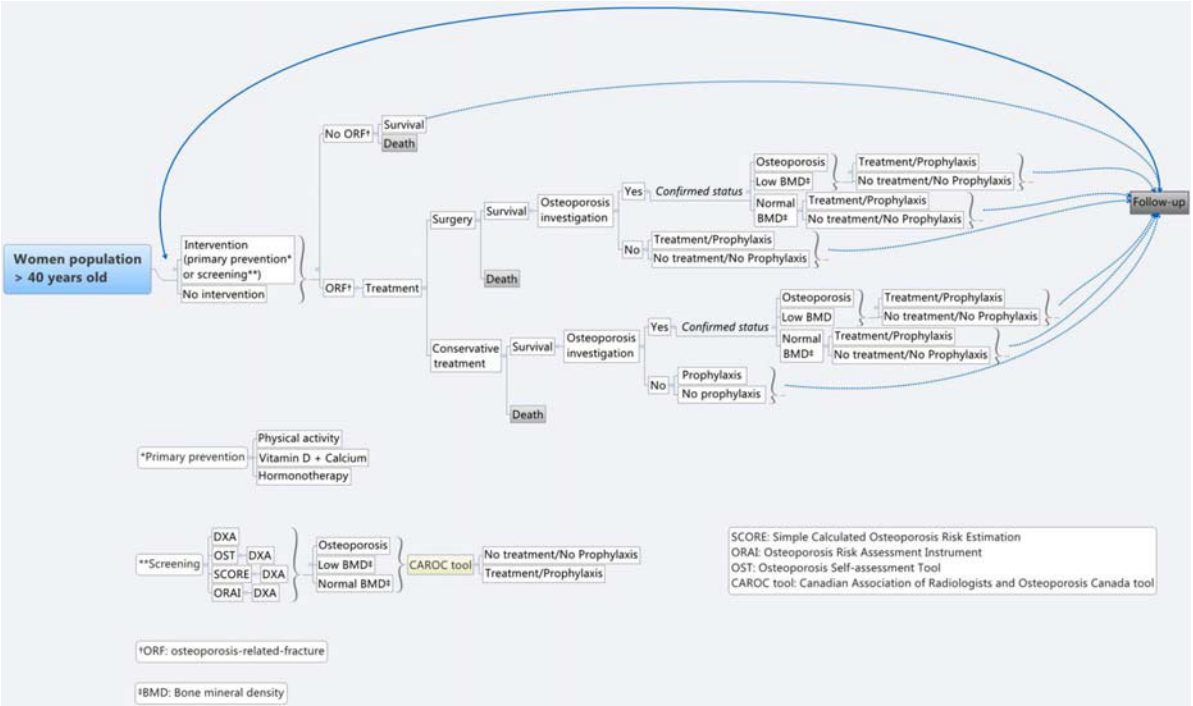

Figure 1

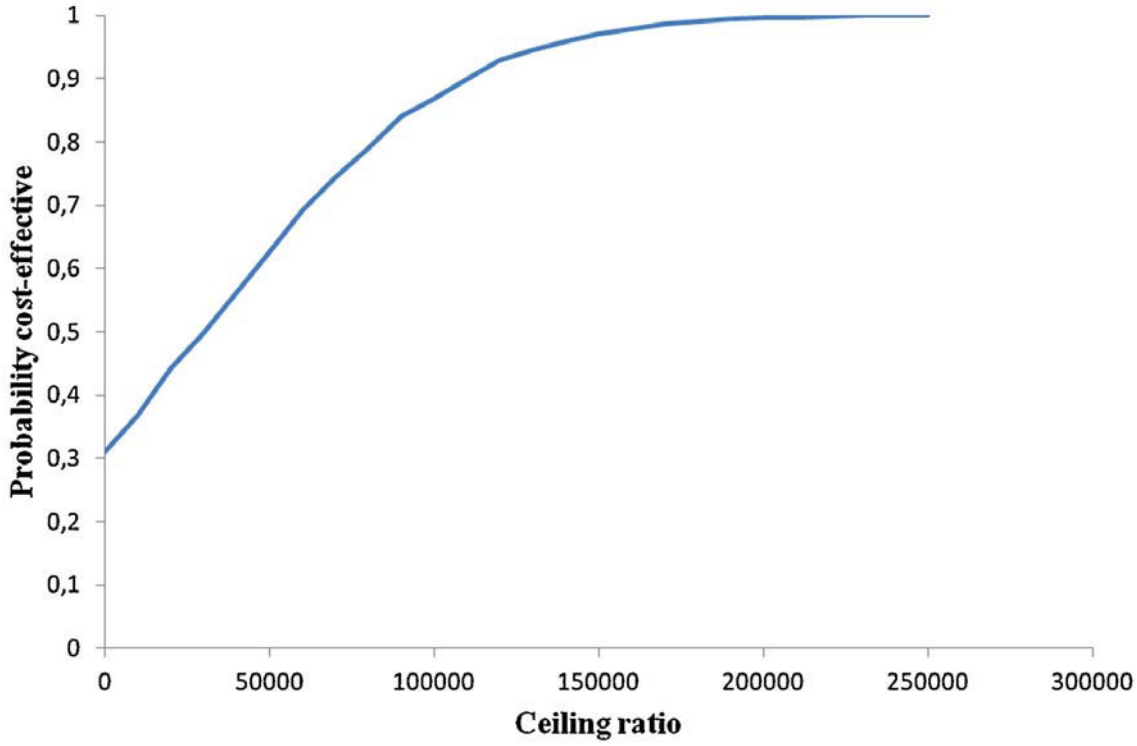

Figure 2

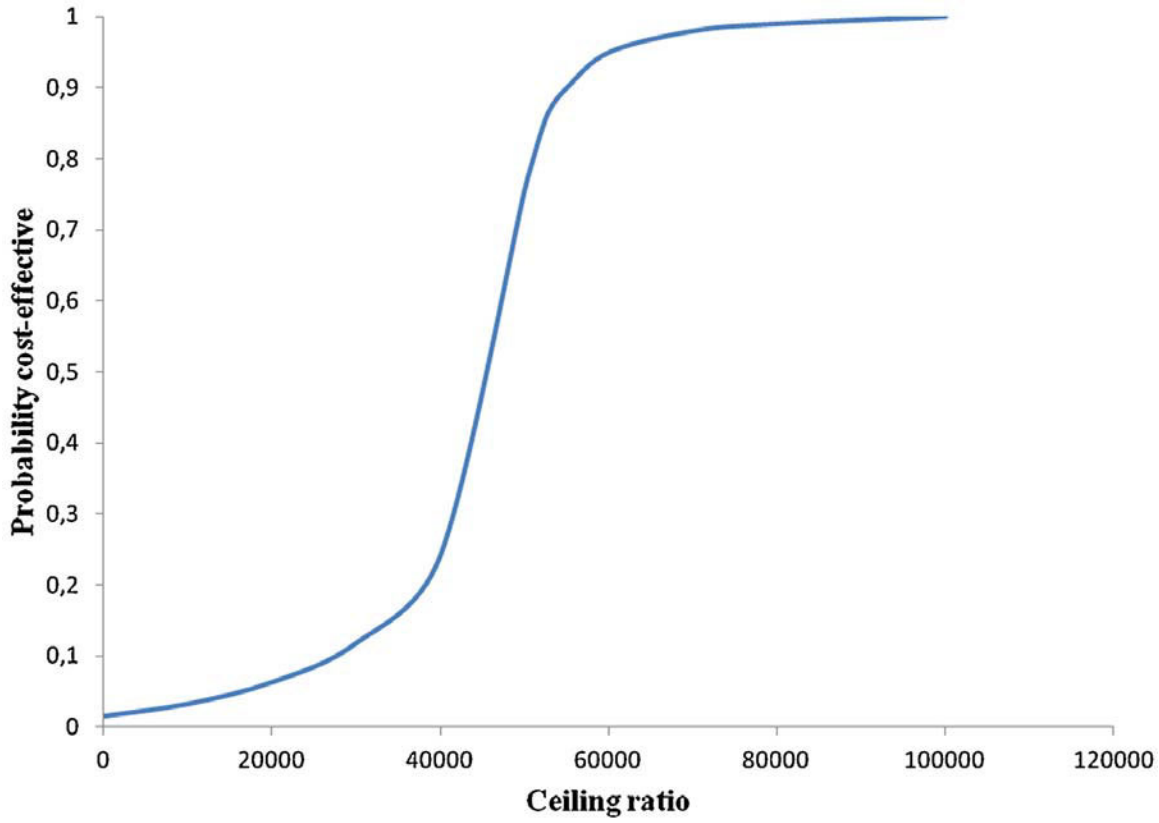

Figure 3