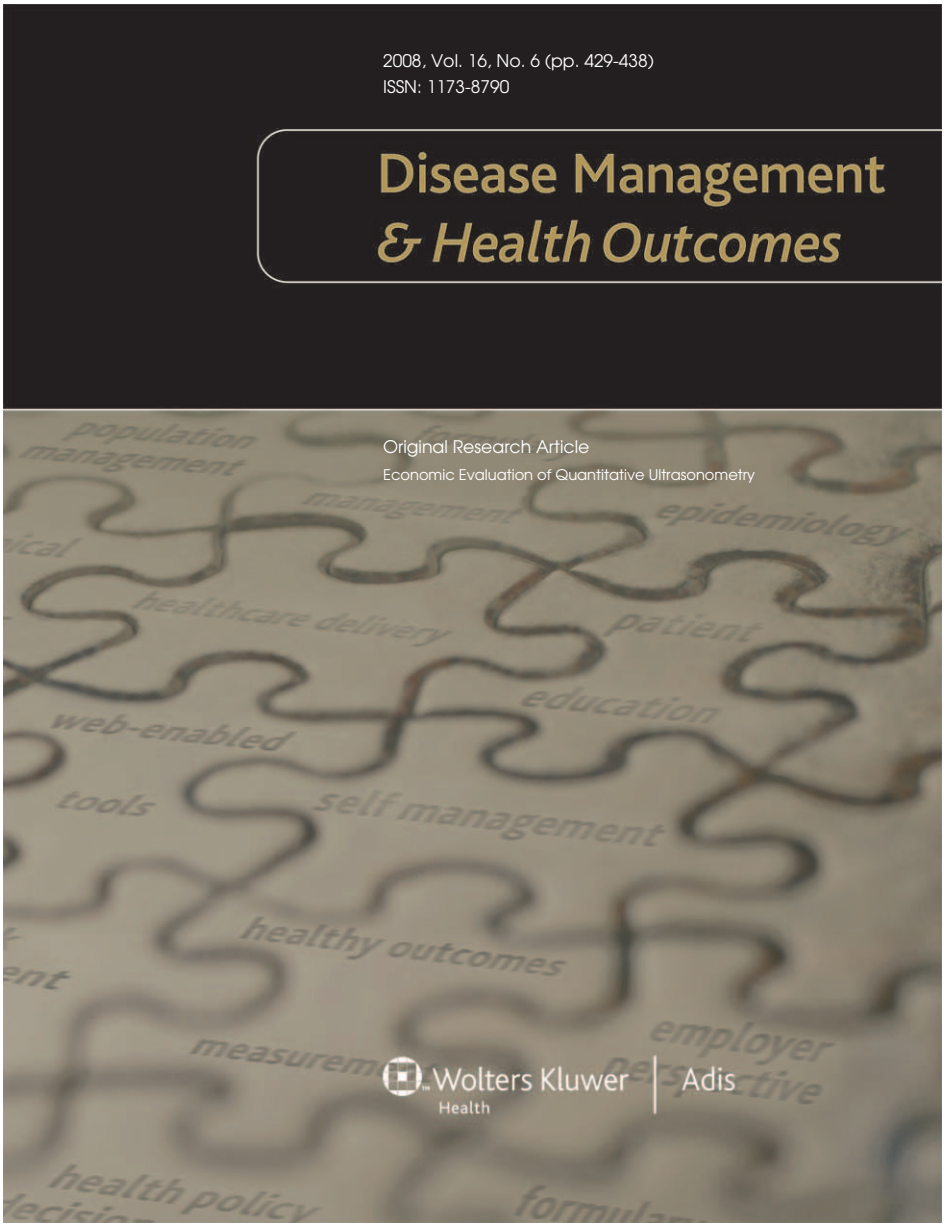

ORIGINAL RESEARCH ARTICLE

Dis Manage Health Outcomes 2008; 16 (6): 429-438
1173-8790/08/0006-0429/$48.00/0

An Economic Evaluation of Quantitative Ultrasonometry as Pre-Screening Test for the Identification of Patients with Osteoporosis

Mickaël Hiligsmann,[1,2] *Olivier Ethgen*,[1] *Olivier Bruyère*[1] and *Jean-Yves Reginster*[1]

1 Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium
2 Department of Economics, University of Liège, Liège, Belgium

Abstract

Background: Screening for osteoporosis has been recommended to identify patients at high risk of fracture in order to provide preventative treatment. Given the limited availability of dual-energy x-ray absorptiometry (DXA) and health resources, quantitative ultrasonometry (QUS) has emerged as an attractive tool for the mass screening scenario. The objective of this study was to evaluate whether a screening strategy using QUS as a pre-screening tool for bone densitometry would be cost effective and, if so, at what cut-off thresholds.

Methods: Decision analytic models were used to compare the cost effectiveness and cost utility of several screening strategies: DXA measurement alone and pre-screening strategies that use different QUS index cut-off thresholds. For each strategy, and for hypothetical cohorts of women, we estimated the number of DXA scans required, the number of osteoporotic patients detected and missed, the total screening cost, and the incremental cost per patient detected. A validated Markov microsimulation model with a lifetime horizon and from a healthcare perspective was also computed in order to estimate the cost per quality-adjusted life-year (QALY) gained of the alternative screening strategies combined with 5 years of alendronate therapy for women who have osteoporosis (T-score −2.5 or less).

Results: The DXA strategy had the highest cost and the highest number of patients with osteoporosis detected. Pre-screening strategies using QUS reduced the number of DXA scans per patient with osteoporosis detected and the total screening cost but they also missed patients with osteoporosis as the QUS index decreased. Pre-screening strategies using QUS T-scores of 0.0, −0.5, −2.0, and −2.5 were dominated by extended dominance, as their incremental cost-effectiveness ratios (ICERs) and incremental cost-utility ratios (ICURs) were higher than that of the next more effective alternative. The cost-effectiveness and cost-utility frontiers included no screening, pre-screening using QUS T-scores of −1.0 and −1.5, and DXA measurement alone.

Conclusion: These results suggest that QUS may be useful as a pre-screening tool for bone densitometry given the limited availability of DXA and health resources, and that the QUS index T-scores of −1.0 and −1.5 are the most appropriate index.

Osteoporosis is an increasingly major health problem around the world. It is a silent disease characterized by low bone mass with microarchitectural disruption and increased skeletal fragility. Osteoporotic fractures are associated with significant morbidity and excess mortality and they represent a substantial economic burden to society. Therefore, screening for osteoporosis has been recommended to identify and treat patients at high risk of fracture, before any fracture occurs.[1-3]

Over the past decade, dual-energy x-ray absorptiometry (DXA) has become the most widely accepted reference method for the diagnosis of osteoporosis.[2] However, DXA does not seem to be adequate for a mass screening scenario because of cost constraints and limited availability.[4,5] Recently, there has been increased interest in the use of quantitative ultrasound (QUS),[6] which has been shown to predict future fracture risk[7-11] and has several potential advantages over DXA for a mass screening scenario. It is portable, less expensive, easy to use (not requiring specially trained personnel), and does not involve ionizing radiation.[6,12] However, there is no consensus regarding diagnostic criteria for osteoporosis using this technique. The WHO definition for osteoporosis was derived in the context of DXA and cannot be applied to QUS.[13,14] Furthermore, few long-term, prospective epidemio-

logical studies have clearly assessed the magnitude of the relationship between low QUS and increased risk of fracture and no clinical trials have evaluated the efficacy of therapies for patients identified by QUS as having high risk of fracture. Therefore, in view of these limitations, it has been suggested that QUS should be used as a selective population pre-screen to reduce the number of patients who require additional DXA testing.[4,15,16]

There is a need for analyses to evaluate whether a screening strategy using calcaneal QUS as a pre-screening tool for bone densitometry would be cost effective and, if so, at what cut-off thresholds and in which populations.[6,17] Therefore, this study was designed to assess the cost effectiveness and cost utility of pre-screening strategies for osteoporosis that use several different QUS index cut-off thresholds. Such an analysis can help physicians and decision makers to determine optimal cut-off thresholds for the QUS index.

Methods

Decision analytic models were used to compare the cost effectiveness and cost utility of several screening strategies: DXA measurement alone and pre-screening strategies that use different QUS index cut-off thresholds. Analyses were performed for Belgian women aged 50–59, 60–69, and 70–79 years. The prevalence of osteoporosis in these age groups was derived from the recommended Third National Health and Nutrition Examination Survey (NHANES III)[18] database, for which young adult bone mineral density values were not significantly different from Belgian estimates.[19] The accuracy of calcaneal QUS at different index cut-off thresholds was assessed in terms of sensitivity and specificity and was obtained from a recent meta-analysis;[6] DXA was used as the reference standard (osteoporosis was defined as a DXA T-score of −2.5 or lower). Sensitivity was defined as the proportion of patients with osteoporosis correctly referred by QUS, and specificity was defined as the proportion of non-osteoporotic patients correctly not referred by QUS. Based on a screening strategy conducted in Belgium, QUS and DXA costs were estimated at €10 and €47 per patient, respectively[20] (DXA costs included the cost of bone densitometry [€27] and the cost of one physician visit [€20] because a physician's prescription is required for a DXA scan) [year 2006 values]. The prevalence of osteoporosis, sensitivity and specificity of the QUS, and DXA costs are shown in table I.

Table I. Sensitivity and specificity of quantitative ultrasonometry (QUS), prevalence of osteoporosis, and screening cost

Accuracy of QUS (sensitivity/specificity)[6]	
QUS T-score of 0.0	0.93/0.24
QUS T-score of −0.5	0.88/0.39
QUS T-score of −1.0	0.79/0.58
QUS T-score of −1.5	0.66/0.74
QUS T-score of −2.0	0.49/0.86
QUS T-score of −2.5	0.33/0.93
Prevalence of osteoporosis[18]	
50–59 y	0.0813
60–69 y	0.1785
70–79 y	0.3394
Screening cost (€)[20]	
DXA	47
QUS	10

DXA = dual-energy X-ray absorptiometry.

Cost-Effectiveness Analysis

A decision tree model (developed in Microsoft® Excel) with a hypothetical cohort of 1000 women was used to estimate, for each screening strategy, the number of DXA scans required, the number of patients with osteoporosis detected, the total screening cost, and the incremental cost-effectiveness ratio (ICER), which is defined as the difference between alternative strategies in terms of total cost, divided by the difference between them in terms of the number of patients with osteoporosis detected (figure 1). It represents the extra cost needed for each additional patient with osteoporosis detected.

Cost-Utility Analysis

Following the cost-effectiveness analysis, a full economic evaluation was performed using the same decision tree model (figure 1) and a validated Markov microsimulation model.[21] The microsimulation model was used to estimate the average lifetime cost and quality-adjusted life-years (QALYs) of three specific populations as shown in figure 1: women with osteoporosis detected (who received drug therapy), women with osteoporosis missed, and women without osteoporosis. Based on these estimates, the proportions of these groups, and on screening costs, we computed the incremental cost-utility ratio (ICUR) of the different screening strategies. An ICUR represents the intervention cost per 1 QALY gained.

The Markov microsimulation model was constructed using decision analysis software (TreeAgePro 2006 Suite, release 0.4, TreeAge Software, Inc.) and used both a lifetime horizon, as recommended for chronic disease,[22] and a Belgian healthcare cost perspective. The model consisted of six health states: no fracture, hip fracture, clinical vertebral fracture, forearm fracture, other fracture, and death (figure 2). 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, QALYs, and costs. All the patients began in the 'no fracture' state, and all the transitions between health states were possible in each cycle and regardless of the current state. If a patient died, she was moved to

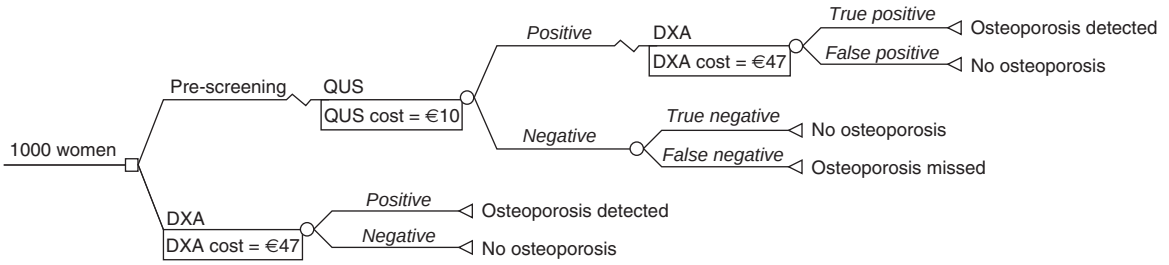

Fig. 1. Decision tree for economic evaluation of screening strategies. **DXA** = dual-energy X-ray absorptiometry; **QUS** = quantitative ultrasonometry.

the 'death' state and remained there for the rest of the simulation. The cycle length was 1 year because fracture events rarely occurred more than once a year and all patients were followed individually until they reached the age of 100 years or died. Each state has its associated costs and QALY, depending on the patient history. Transition costs included direct and indirect fracture costs. Long-term costs beyond the first year after hip fracture were assigned for women in a nursing home and the disutility associated with fractures was modeled as a relative reduction in QALY. Discount rates of 3% and 1.5% were assumed for costs and health benefits, respectively.[22]

A Markov microsimulation model was chosen because such models began to supplant cohort-based models in healthcare decision making because of the desire to avoid an unmanageable number of health states.[23] By simulating one patient at a time, the patient's history (such as prior fractures and current residential status) can be recorded by so-called 'tracker' variables and used in calculations of transition probabilities, utilities, and costs. Therefore, these models are more able to represent the complexity and heterogeneity of a pathology such as osteoporosis,[24,25] and increase the reliability of economic evaluations in osteoporosis.

The incidence rates of first fracture in the general population were estimated for each type of fracture.[26] We incorporated an increased relative risk for a subsequent fracture after a prior fracture of the same type[27] and for a hip fracture after a vertebral fracture.[28] All these increased relative risks were increased by a factor of 1.7 during the year following the fracture,[29] except in the case of vertebral fracture (for which the increased fracture risk was not increased during the year following the fracture), and were reduced by 10% per decade.[30]

Fracture risk was estimated for women with osteoporosis by multiplying the fracture risk in the general population with a relative risk factor. The relative risk was calculated from the bone mineral density (BMD), using a previously described method.[31] The number of standard deviations of BMD below the age-matched average BMD was derived from the recommended NHANES III[18] database and it was assumed that one standard deviation decrease in BMD was associated with a relative risk of 2.6, 1.8, 1.4, and 1.6 for hip, clinical vertebral, forearm, and other osteoporotic fracture, respectively.[32] A recent study showed that the relative risk decreased with age for hip fracture and ranged from 3.68 (at 50 years) to 1.93 (at 85 years).[33] These values were only used when they were lower than 2.6.

Background mortality was taken from an official source.[34] Hip and clinical vertebral fracture were associated with a mortality increase.[35-39] Excess mortality in the first and following years after a fracture was derived from the study of Oden et al.[35] Because excess mortality may be attributable to co-morbidities, a conservative assumption was made that only 25% of the excess mortality could be directly or indirectly attributable to the fractures themselves.[38,39]

Utilities for the general population, as well as relative reductions due to fractures, were derived from a systematic review, which suggested reference values for countries that do not have their own database (table II).[40] It was also assumed that, when a second or further fracture occurs at the same site, the long-term effect of previous fractures is reduced by half, in line with recent studies showing that the number of fractures is a significant determinant of quality of life.[41-44] For an individual with both a hip and a vertebral clinical fracture, the total impact on QALY was assumed to be equal to the sum of the impacts related to each of the fractures.[44]

Fracture costs (estimated in €, year 2006 values) can be divided into acute costs (direct and indirect) during the first year following the fracture, and long-term costs, which persist for the rest of the patient's lifetime (table II). Direct hip fracture costs, including hospitalization and extra costs during the year following the fracture, ranged from €16 457 to €20 998.[45,46] Forearm fracture costs were €2159.[49] The costs of clinical vertebral and

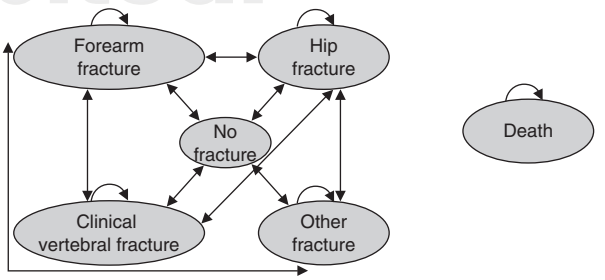

Fig. 2. Structure of the Markov microsimulation model. Transitions to death may occur from any state (arrows to the death state are excluded from the figure for simplification).

Table II. Utilities and fracture costs (€)

Parameter	Values
QALY[40]	
General population (50–60, 60–70, 70–80, >80 y)	0.859, 0.827, 0.762, 0.711
QALY disutility due to fracture[40]	First year/subsequent years
hip fracture	0.203, 0.101
clinical vertebral fracture	0.280, 0.069
forearm fracture	0.060, 0
other fracture	0.090, 0
Direct fracture costs	
Hip fracture (first year cost)[45,46]	From 16 457 to 20 998
Hip fracture (yearly long-term cost)[45]	From 991 (50–59 y) to 4575 (90–100 y)
Clinical vertebral fracture[47,48]	2429
Forearm fracture[49]	2159
Other fracture[47,48]	3573
Indirect fracture costs[50-52]	
Hip fracture	From 6626 (50–54 y) to 1062 (60–64 y)
Clinical vertebral fracture	From 2834 to 454
Forearm fracture	From 1804 to 289
Other fracture	From 2418 to 387

QALY = quality-adjusted life-year.

other fractures were estimated at €2429 and €3573, respectively, assuming that they represent 17% and 25%, respectively, of hip fracture cost.[47,48] Hip fracture costs for the second and subsequent years were based on the proportion of patients being institutionalized following the fracture, and ranged from 5% to 30%.[45] The annual cost of being in a nursing home was reduced by the probability of being institutionalized later in life, regardless of the hip fracture. Indirect costs were estimated by multiplying the proportion of productivity loss due to fractures[50] by workforce participation rates[51] and by the average annual wage for employed women.[52]

It was assumed that treated women received 5 years of alendronate therapy, the most widely presented osteoporosis treatment worldwide. A meta-analysis suggested that alendronate therapy reduced the risk of fracture by 38%, 44%, 33%, and 19% for hip, clinical vertebral, forearm, and other fracture, respectively.[53] After the treatment period, it was assumed that the effect of treatment reduced linearly during the same duration as therapy. Realistic persistence level was incorporated into the model. In a recent study assessing adherence to biphosphonates, including alendronate,[54] only 70%, 58%, 40%, 25%, and 20% of patients were found to be persistent with treatment after 3 months, 6 months, 1 year, 2 years, and 5 years of therapy, respectively. Therefore, we assumed that 30%, 12%, 18%, and 15% of patients stopped drug therapy after 3 months, 6 months, 1 year, and 2 years, respectively. No treatment effect was assumed for patients who stopped treatment after 3 months.

The cost of treatment included drug costs and costs of assessment. The annual cost of alendronate therapy was estimated at €421.18 (Fosamax® [1], 70-mg tablet packages, once per week). Most of the women treated with alendronate therapy received calcium and vitamin D supplementation.[55,56] Therefore, the analysis also included the annual cost of calcium and vitamin D (€51.37). It was also assumed that treatment was associated with a once-yearly physician's visit (€20) and an additional bone densitometry measurement in years 3 and 5 (estimated at €47).

A univariate sensitivity analysis was performed to test the robustness of the outcomes of the cost-utility analysis. The baseline parameter values for screening cost, discount rates, fracture risk, fracture disutility, fracture cost, treatment cost, treatment efficacy, and medication non-adherence were varied over plausible ranges to explore the impact of different parameter values on the results.

The developed model has been validated in a previous study.[21] The predictive validity of our model was assessed in terms of its ability to estimate life expectancy and lifetime absolute risk of fracture. First, differences between estimated and published life expectancies were very small (<0.005 years). Second, absolute lifetime risks of fracture estimates are within the range of previous estimates.[26] Furthermore, we have performed sensitivity analyses

1 The use of trade names is for product identification purposes only and does not imply endorsement.

in terms of model parameters and modeling assumptions and all of these analyses were coherent with expected conclusions.

Results

Cost-Effectiveness Analysis

Outcomes of the different screening strategies are shown in table III. By performing DXA scans in all women, the DXA strategy detected all women with osteoporosis and was, therefore, associated with the highest number of patients with osteoporosis detected. This strategy also had the highest number of DXA scans required per patient detected and the highest total cost. Pre-screening strategies using QUS reduced the number of patients who required additional DXA testing. Therefore, the number of DXA scans required per patient detected and the total costs were lower than for the DXA strategy. However, the number of patients with osteoporosis detected was also lower because of false negative results.

A lower QUS index cut-off threshold was associated with a decrease in the total number of DXA scans required, in the number of DXA scans required per patient detected, and in the total cost. But a lower QUS index cut-off threshold increased the number of women with osteoporosis missed, estimated at 7%, 12%, 21%, 34%, 51%, and 67% of all women with osteoporosis for QUS T-scores of 0.0, −0.5, −1.0, −1.5, −2.0, and −2.5, respectively. Increasing population prevalence increased the number of patients detected and the number of patients missed with pre-screening

Table III. Outcomes of the different screening strategies for a population of 1000 women

Screening strategy	DXA (n)[a]	Patients detected (n)[b]	DXA required per patient detected (n)	Total cost[c] (€)	ICER[d]
Age 50–59 y					
QUS T-score of −2.5	91	27	3.40	14 283	Dominated[e]
QUS T-score of −2.0	168	40	4.23	17 917	Dominated
QUS T-score of −1.5	293	54	5.45	23 748	443
QUS T-score of −1.0	450	64	7.01	31 154	701
QUS T-score of −0.5	632	72	8.83	39 701	Dominated
QUS T-score of 0.0	774	76	10.23	46 370	Dominated
DXA	1000	81	12.30	47 000	928
Age 60–69 y					
QUS T-score of −2.5	116	59	1.98	15 471	Dominated
QUS T-score of −2.0	202	87	2.31	19 516	Dominated
QUS T-score of −1.5	331	118	2.81	25 576	217
QUS T-score of −1.0	486	141	3.45	32 844	313
QUS T-score of −0.5	658	157	4.19	40 935	Dominated
QUS T-score of 0.0	790	166	4.76	47 146	Dominated
DXA	1000	178	5.60	47 000	378
Age 70–79 y					
QUS T-score of −2.5	158	112	1.41	17 437	Dominated
QUS T-score of −2.0	259	166	1.56	22 163	Dominated
QUS T-score of −1.5	396	224	1.77	28 601	128
QUS T-score of −1.0	546	268	2.03	35 642	Dominated
QUS T-score of −0.5	702	299	2.35	42 977	Dominated
QUS T-score of 0.0	818	316	2.59	48 432	Dominated
DXA	1000	339	2.95	47 000	159

a Number of women with a positive QUS result.

b Prevalence × sensitivity.

c No. of QUS × QUS cost (€10) + no. of DXA × DXA cost (€47).

d ICER is calculated for each successive alternative, from the least costly to the most.

e A strategy is dominated as its ICER is higher than the next more effective alternative.

DXA = dual-energy x-ray absorptiometry; **ICER** = incremental cost-effectiveness ratio (cost in € per patient detected); **QUS** = quantitative ultrasonometry.

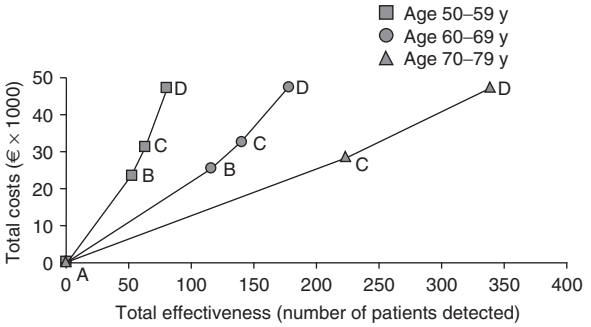

Fig. 3. Total costs and effectiveness of the different screening strategies (for 1000 women). The incremental cost-effectiveness ratios are given by the slope of the line joining any two points. Dominated strategies were excluded from the graph. **A** = no screening; **B** = quantitative ultrasonometry (QUS) T-score of −1.5; **C** = QUS T-score of −1.0; **D** = dual-energy x-ray absorptiometry (DXA).

strategies and decreased the number of DXA scans required per patient detected.

The ICERs were calculated for each mutually exclusive screening strategy, from the least costly to the most. In figure 3, the ICERs were given by the slope of the line joining any two points (alternatives). Pre-screening strategies using QUS T-scores of 0.0, −0.5, −2.0, and −2.5 were eliminated because of extended dominance, as their ICERs were higher than that of the next more effective alternative.[57] After exclusion of the dominated strategies, the ICERs were recalculated. The strategies forming the cost-effectiveness frontier included no screening, pre-screening strategies using QUS T-scores of −1.0 and −1.5, and DXA measurement alone. For women aged 70–79 years, a QUS T-score of −1.0 was also dominated.

Cost-Utility Analysis

Lifetime costs, QALYs, and the ICUR for the screening strategies are shown in table IV for different starting ages. The DXA strategy had the highest lifetime cost and QALYs. Pre-screening strategies were associated with a decrease in lifetime cost and effectiveness as the QUS index decreased. The ICURs were calculated for each successive alternative, from the least to the most costly and were given by the slope of the line joining any two points on figure 4. Dominated strategies were excluded from the graph and removed from the sequence before calculating the ICURs.

Table V shows the results of the univariate sensitivity analyses. Screening cost was an important model parameter. Assuming a 20% reduction of DXA cost, only the pre-screening strategy using a QUS T-score of −1.5 was not dominated, while all pre-screening strategies using QUS were dominated assuming a DXA cost of €27. Changes in other parameters did not affect the strategies forming the cost-utility frontier but did modify the ICURs. Increases in the cost per QALY gained were observed when assuming higher discount rates, lower fracture disutility, lower fracture costs, and lower fracture risk. The cost per QALY gained was also shown to be greater for higher treatment cost and lower treatment efficacy.

Discussion and Conclusions

QUS is increasingly used as a selective population pre-screen to reduce the number of patients who require additional DXA testing. Some previous studies[17,58-60] have suggested that screening with QUS is cost effective relative to clinical criteria and DXA. In contrast, other studies[61,62] have suggested that QUS assessment does not appear to be cost effective as a pre-screen for DXA. The main reason for this discrepancy lies in the differences between DXA and QUS costs. However, these studies were limited in that they restricted the measurement of effectiveness to the number of cases detected. Although useful, this kind of measurement does not necessarily show the full effectiveness of a program, as it reflects process rather than final outcome.[17] The current study assessed the cost effectiveness and the cost utility of screening strategies using QUS as pre-screening for bone densitometry. Moreover, we have compared several different QUS index cut-off thresholds in order to help physicians and decision makers to determine optimal cut-off thresholds for the QUS index.

From our analysis, it appears that pre-screening strategies were useful in reducing the number of DXAs required per patient detected, and the total screening cost, but missed patients with osteoporosis. The choice of the QUS index T-score also had a significant impact on the results. In fact, researchers have suggested several QUS cut-off thresholds, including QUS threshold T-scores of 0.0, −1.0, −1.5, and −2.5.[13,14,63,64] However, there are no universal rules and clinicians may use these or other thresholds to identify patients who require additional DXA scans. In our study, QUS T-scores of 0.0, −0.5, −2.0, and −2.5 were dominated by extended dominance and, therefore, should not be recommended. Only the strategies forming the cost-effectiveness and cost-utility frontiers (i.e. no screening, pre-screening using QUS T-scores of −1.0 and −1.5, and DXA measurement alone) are potential candidates for decision making that depends on the willingness to pay (WTP) for a unit of effectiveness and/or the available total budget. In Belgium, there are actually no ICER threshold values for policy decisions.

So, irrespective of other concerns (e.g. feasibility, available total budget), for women aged 60–69 years, the best screening options are no screening for a WTP lower than €33 466 per QALY; pre-screening with QUS for a WTP between €33 466 and €41 181; and DXA measurement alone for a WTP above €41 181. Screening for osteoporosis should not be recommended for all women aged <60 years given the high ICERs. For women aged ≥70 years, pre-screening with QUS is the preferred strategy

in a very narrow range (€17 831–19 301 per QALY). Therefore, DXA measurement alone should be preferred for these women.

These results have been generated without considering DXA availability and healthcare budgets. In real life, limited availability of DXA and healthcare budgets play a critical role in healthcare decision making and in the choice of screening strategy. Although a health policy of making DXA more widely available would be worthwhile, pre-screening with QUS seems an alternative option where budget is a constraint, and in particular for women aged 60–69 years and for women aged 50–59 years in whom the risk factor profile suggests cause for concern. Sensitivity analyses also showed that QUS and DXA costs were of great importance. Therefore, efforts should be made to reduce screening costs, and the discrepancy between QUS and DXA costs may affect the choice of the screening strategy.

There are some potential limitations of our analysis. First, QUS and DXA are not highly correlated. Thus, a screening strategy with QUS as pre-screening for bone densitometry may not be the most efficient way to screen for osteoporosis.[6] Further research is needed to assess whether QUS would be used as an alternative method to DXA and to evaluate the outcomes of screening strategies involving QUS alone. Second, DXA is also an imperfect reference standard for identifying individuals at risk of fracture. Many fractures occur in women who have BMD T-scores greater than −2.5, the threshold for osteoporosis.[65-67] Therefore, comparing QUS with an imperfect DXA reference standard may underestimate its potential usefulness for osteoporosis screening.[6] How-

Table IV. Lifetime costs, quality-adjusted life-years (QALYs) and incremental cost-utility ratios (ICURs) of the different screening strategies

Screening strategy	Lifetime costs (€)	Lifetime QALYs	ICUR (€ per QALY gained)[a]
Age 55 y			
No screening	4889	18.2759	NA
QUS T-score of −2.5	4923	18.2763	Dominated[b]
QUS T-score of −2.0	4935	18.2765	Dominated
QUS T-score of −1.5	4951	18.2767	75 073
QUS T-score of −1.0	4966	18.2769	92 010
QUS T-score of −0.5	4979	18.2770	Dominated
QUS T-score of 0.0	4989	18.2771	Dominated
DXA	4993	18.2772	106 938
Age 65 y			
No screening	6414	13.0600	NA
QUS T-score of −2.5	6458	13.0612	Dominated
QUS T-score of −2.0	6475	13.0618	Dominated
QUS T-score of −1.5	6496	13.0624	33 466
QUS T-score of −1.0	6515	13.0629	38 085
QUS T-score of −0.5	6530	13.0632	Dominated
QUS T-score of 0.0	6541	13.0634	Dominated
DXA	6547	13.0637	41 181
Age 75 y			
No screening	7318	8.0565	NA
QUS T-score of −2.5	7355	8.0584	Dominated
QUS T-score of −2.0	7369	8.0593	Dominated
QUS T-score of −1.5	7385	8.0603	Dominated
QUS T-score of −1.0	7400	8.0610	17 831
QUS T-score of −0.5	7413	8.0615	Dominated
QUS T-score of 0.0	7421	8.0618	Dominated
DXA	7424	8.0622	19 707

a ICUR is calculated for each successive alternative, from the least costly to the most.

b A strategy is dominated as its incremental cost-effectiveness ratio is higher than the next more effective alternative.

DXA = dual-energy x-ray absorptiometry; **NA** = not applicable; **QUS** = quantitative ultrasonometry.

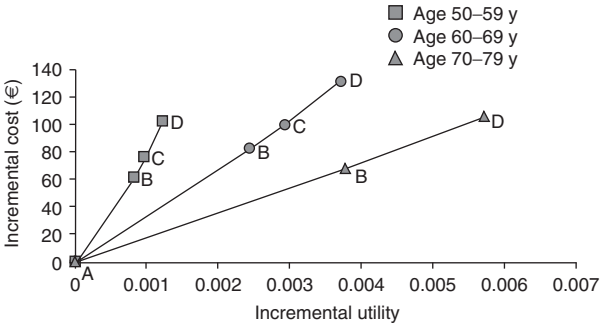

Fig. 4. Incremental cost and utility of the different screening strategies. The incremental cost-utility ratios are given by the slope of the line joining any two points. Dominated strategies were excluded from the graph. **A** = no screening; **B** = quantitative ultrasonometry (QUS) T-score of −1.5; **C** = QUS T-score of −1.0; **D** = dual-energy x-ray absorptiometry (DXA).

ever, DXA remains the best single predictor for fracture risk assessment today. A combination of clinical risk factors and DXA measurement may significantly improve the calculation of the future absolute risk (10 year) for a single individual. Currently, there are no tools available in daily practice that can accurately measure the other components of skeletal fragility (i.e. determinants of bone strength).

A third limitation is that the accuracy of QUS was only based on studies that evaluated the sensitivity and specificity of calcaneal QUS measurement.[6] Therefore, the results would not be applicable to other skeletal sites. Fourth, no sensitivity analyses were performed on specificity and sensibility of QUS index T-scores. Our analysis was based on the results of a recent meta-analysis.[6] Fifth, other pre-screening tests for identification of patients with osteoporosis are available and include the FRAX™ tool, the International Osteoporosis Foundation 'one-minute-risk' test, and several validated questionnaires.[68] It would be worthwhile to assess the cost utility of these tools and to compare it with QUS.

In conclusion, this article suggests that QUS may be useful as a pre-screening tool for bone densitometry given the limited availability of DXA and health resources and that the QUS index T-scores of −1 and −1.5 are the most appropriate index. As aforementioned in this section, further research is needed to assess whether QUS could be used as an alternative method to DXA and to evaluate the outcomes of screening strategies involving QUS alone.

Table V. Incremental cost-utility ratios (ICURs)[a] of the different screening strategies: univariate sensitivity analyses for women aged 60–69 y

Sensitivity analysis	ICUR of each screening strategy (€ per QALY gained)		
	QUS T-score of −1.5[b]	QUS T-score of −1.0	DXA
Base case	33 466	38 085	41 181
DXA cost 20% lower	32 283	Dominated	34 965
DXA cost 20% higher	34 733	40 615	46 422
DXA cost €27	Dominated	Dominated	28 506
QUS cost 20% lower	32 803	37 830	43 065
QUS cost 20% higher	34 312	37 830	38 322
Discount rates 5%	58 612	66 303	71 456
0.8 times base-case fracture risk	45 688	51 212	54 914
1.2 times base-case fracture risk	23 439	27 122	29 590
0.8 times base-case fracture disutility	39 671	44 651	47 989
1.2 times base-case fracture disutility	29 901	34 117	36 942
0.8 times base-case fracture cost	38 771	43 726	47 046
1.2 times base-case fracture cost	28 506	33 127	36 225
Treatment cost 20% higher	26 104	30 638	33 677
Treatment cost 20% lower	42 492	46 861	49 789
Treatment efficacy 20% higher	20 797	24 023	26 184
Treatment efficacy 20% lower	42 745	47 859	51 285
Optimal persistence assumption	25 016	26 676	27 789

a After exclusion of the dominated strategies (not included in the table), ICURs are calculated for each successive alternative, from the least costly to the most.

b Compared with no screening strategy.

DXA = dual-energy x-ray absorptiometry; **QALY** = quality-adjusted life-year: **QUS** = quantitative ultrasonometry.

Acknowledgments

J.-Y. Reginster has received consulting fees, lecture fees, and grant support from, and served on paid advisory boards for, various pharmaceutical companies.

The other authors have no conflicts of interest that are directly relevant to the content of this study. No sources of funding were used to assist in the preparation of this study.

References

1. US Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Ann Intern Med 2002; 137: 526-8
2. Kanis J, Burlet N, Cooper C, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008; 19: 429-35
3. National Osteoporosis Foundation. Clinician’s guide to prevention and treatment of osteoporosis. Washington, DC: NOF, 2008
4. Boonen S, Nijs J, Borghs H, et al. Identifying postmenopausal women with osteoporosis by calcaneal ultrasound, metacarpal digital X-ray radiogrammetry and phalangeal radiographic absorptiometry: a comparative study. Osteoporos Int 2005; 16: 93-100
5. Ben Sedrine W, Broers P, Devogelaer JP, et al. Interest of a prescreening questionnaire to reduce the cost of bone densitometry. Osteoporos Int 2002; 13: 434-42
6. Nayak S, Olkin I, Liu H, et al. Meta-analysis: accuracy of quantitative ultrasound for identifying patients with osteoporosis. Ann Intern Med 2006; 144: 832-41
7. Bauer DC, Ewing SK, Cauley JA, et al. Quantitative ultrasound predicts hip and non-spine fracture in men: the MrOS study. Osteoporos Int 2007; 18: 771-7
8. Bauer DC, Gluer CC, Cauley JA, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med 1997; 157: 629-34
9. Khaw KT, Reeve J, Luben R, et al. Prediction of total and hip fracture risk in men and women by quantitative ultrasound of the calcaneus: EPIC-Norfolk prospective population study. Lancet 2004; 363: 197-202
10. Hans D, Dargent-Molina P, Schott AM, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. Lancet 1996; 348: 511-4
11. Reginster JY, Dethor M, Pirenne H, et al. Reproducibility and diagnostic sensitivity of ultrasonometry of the phalanges to assess osteoporosis. Int J Gynaecol Obstet 1998; 63: 21-8
12. Wuster C, Heilmann P, Pereira-Lima J, et al. Quantitative ultrasonometry (QUS) for the evaluation of osteoporosis risk: reference data for various measurement sites, limitations and application possibilities. Exp Clin Endocrinol Diabetes 1998; 106: 277-88
13. Damilakis J, Perisinakis K, Gourtsoyiannis N. Imaging ultrasonometry of the calcaneus: optimum T-score thresholds for the identification of osteoporotic subjects. Calcif Tissue Int 2001; 68: 219-24
14. Frost ML, Blake GM, Fogelman I. Can the WHO criteria for diagnosing osteoporosis be applied to calcaneal quantitative ultrasound? Osteoporos Int 2000; 11: 321-30
15. Kraemer DF, Nelson HD, Bauer DC, et al. Economic comparison of diagnostic approaches for evaluating osteoporosis in older women. Osteoporos Int 2006; 17: 68-76
16. Dargent-Molina P, Piault S, Breart G. A comparison of different screening strategies to identify elderly women at high risk of hip fracture: results from the EPIDOS prospective study. Osteoporos Int 2003; 14: 969-77
17. Marin F, Lopez-Bastida J, Diez-Perez A, et al. Bone mineral density referral for dual-energy X-ray absorptiometry using quantitative ultrasound as a prescreening tool in postmenopausal women from the general population: a cost-effectiveness analysis. Calcif Tissue Int 2004; 74: 277-83
18. Looker AC, Orwoll ES, Johnston CC, et al. Prevalence of low femoral bone density in older US adults from NHANES III. J Bone Miner Res 1997; 12: 1761-8
19. Boonen S, Kaufman JM, Reginster JY, et al. Patient assessment using standardized bone mineral density values and a national reference database: implementing uniform thresholds for the reimbursement of osteoporosis treatments in Belgium. Osteoporos Int 2003; 14: 110-5
20. Hiligsmann M, Bruyère O, Pire G, et al. Economic evaluation of osteoporosis screening strategy conducted in the Province of Liège with the cooperation of Liège Province Santé [in French]. Rev Med Liege 2008; 63: 588-94
21. Hiligsmann M, Ethgen O, Bruyère O, et al. Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. Value Health. In press.
22. Cleemput I, Crott R, Vrijens F, et al. Recommandations provisoires pour les évaluations pharmaco-économiques en Belgique. Health Technology Assessment (HTA) [KCE reports 78B (D/2008/10.273/24)]. Bruxelles: Centre Fédéral d’Expertise des Soins de Santé (KCE), 2008
23. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics 2006; 24 (11): 1043-53
24. Kanis JA, Brazier JE, Stevenson M, et al. Treatment of established osteoporosis: a systematic review and cost-utility analysis. Health Technol Assess 2002; 6: 1-146
25. Vanness DJ, Tosteson AN, Gabriel SE, et al. The need for microsimulation to evaluate osteoporosis interventions. Osteoporos Int 2005; 16: 353-8
26. Hiligsmann M, Bruyère O, Ethgen O, et al. Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women. Bone 2008; 43: 991-94
27. Klotzbuecher CM, Ross PD, Landsman PB, et al. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 2000; 15: 721-39
28. Black DM, Arden NK, Palermo L, et al. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures: study of Osteoporotic Fractures Research Group. J Bone Miner Res 1999; 14: 821-8
29. Johnell O, Kanis JA, Oden A, et al. Fracture risk following an osteoporotic fracture. Osteoporos Int 2004; 15: 175-9
30. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004; 35: 375-82
31. Kanis JA, Johnell O, Oden A, et al. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. Bone 2000; 27: 585-90
32. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996; 312: 1254-9
33. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res 2005; 20: 1185-94
34. Directorate-general Statistics and Economic Information. Mortality tables 2004 and 2002-2004. Brussels: FPS Economy, 2006
35. Oden A, Dawson A, Dere W, et al. Lifetime risk of hip fractures is underestimated. Osteoporos Int 1998; 8: 599-603
36. Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. Osteoporos Int 2000; 11: 556-61
37. Johnell O, Kanis JA, Oden A, et al. Mortality after osteoporotic fractures. Osteoporos Int 2004; 15: 38-42
38. Kanis JA, Oden A, Johnell O, et al. Excess mortality after hospitalisation for vertebral fracture. Osteoporos Int 2004; 15: 108-12
39. Kanis JA, Oden A, Johnell O, et al. The components of excess mortality after hip fracture. Bone 2003; 32: 468-73
40. Hiligsmann M, Ethgen O, Richy F, et al. Utility values associated with osteoporotic fracture: a systematic review of the literature. Calcif Tissue Int 2008; 82: 288-92
41. Fechtenbaum J, Cropet C, Kolta S, et al. The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women. Osteoporos Int 2005; 16: 2175-9
42. Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 2000; 15: 1384-92
43. Silverman SL, Minshall ME, Shen W, et al. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. Arthritis Rheum 2001; 44: 2611-9
44. Tosteson AN, Gabriel SE, Grove MR, et al. Impact of hip and vertebral fractures on quality-adjusted life years. Osteoporos Int 2001; 12: 1042-9
45. Reginster JY, Gillet P, Ben Sedrine W, et al. Direct costs of hip fractures in patients over 60 years of age in Belgium. Pharmacoeconomics 1999; 15 (5): 507-14
46. Autier P, Haentjens P, Bentin J, et al. Costs induced by hip fractures: a prospective controlled study in Belgium: Belgian Hip Fracture Study Group. Osteoporos Int 2000; 11: 73-80

47. Gabriel SE, Tosteson AN, Leibson CL, et al. Direct medical costs attributable to osteoporotic fractures. Osteoporos Int 2002; 13: 323-30
48. Melton 3rd LJ, Gabriel SE, Crowson CS, et al. Cost-equivalence of different osteoporotic fractures. Osteoporos Int 2003; 14: 383-8
49. Bouee S, Lafuma A, Fagnani F, et al. Estimation of direct unit costs associated with non-vertebral osteoporotic fractures in five European countries. Rheumatol Int 2006; 26: 1063-72
50. Meerding WJ, Looman CW, Essink-Bot ML, et al. Distribution and determinants of health and work status in a comprehensive population of injury patients. J Trauma 2004; 56: 150-61
51. SMEs, independent professions and energy, labour force survey. Brussels: FPS Economy, 2004
52. Directorate-general Statistics and Economic Information. Structure and distribution of earnings survey. Brussels: FPS Economy, 2007
53. Stevenson M, Jones ML, De Nigris E, et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess 2005; 9 (22): 1-160
54. Rabenda V, Mertens R, Fabri V, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int 2008; 19: 811-8
55. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348: 1535-41
56. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab 2000; 85: 4118-24
57. Drummond M, O'Brien B, Stoddart G, et al. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford University Press: Oxford, 2005
58. Langton CM, Ballard PA, Langton DK, et al. Maximising the cost effectiveness of BMD referral for DXA using ultrasound as a selective population pre-screen. Technol Health Care 1997; 5: 235-41
59. Langton CM, Langton DK, Beardsworth SA. Comparison of accuracy and cost effectiveness of clinical criteria and BUA for referral for BMD assessment by DXA in osteoporotic and osteopenic perimenopausal subjects. Technol Health Care 1999; 7: 319-30
60. Lippuner K, Fuchs G, Ruetsche AG, et al. How well do radiographic absorptiometry and quantitative ultrasound predict osteoporosis at spine or hip? A cost-effectiveness analysis. J Clin Densitom 2000; 3: 241-9
61. Sim MF, Stone M, Johansen A, et al. Cost effectiveness analysis of BMD referral for DXA using ultrasound as a selective pre-screen in a group of women with low trauma Colles' fractures. Technol Health Care 2000; 8: 277-84
62. Sim MF, Stone MD, Phillips CJ, et al. Cost effectiveness analysis of using quantitative ultrasound as a selective pre-screen for bone densitometry. Technol Health Care 2005; 13: 75-85
63. Lopez-Rodriguez F, Mezquita-Raya P, de Dios Luna J, et al. Performance of quantitative ultrasound in the discrimination of prevalent osteoporotic fractures in a bone metabolic unit. Bone 2003; 32: 571-8
64. Hans D, Hartl F, Krieg MA. Device-specific weighted T-score for two quantitative ultrasounds: operational propositions for the management of osteoporosis for 65 years and older women in Switzerland. Osteoporos Int 2003; 14: 251-8
65. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med 2004; 164: 1108-12
66. Wainwright SA, Marshall LM, Ensrud KE, et al. Hip fracture in women without osteoporosis. J Clin Endocrinol Metab 2005; 90: 2787-93
67. Cranney A, Jamal SA, Tsang JF, et al. Low bone mineral density and fracture burden in postmenopausal women. CMAJ 2007; 177 (6): 575-80
68. Richy F, Gourlay M, Ross PD, et al. Validation and comparative evaluation of the osteoporosis self-assessment tool (OST) in a Caucasian population from Belgium. QJM 2004; 97 (1): 39-46

About the Author: Mickaël Hiligsmann, MSc, MPH, is currently a teaching assistant at the Department of Economics at the University of Liège and a PhD student at the Department of Public Health, Epidemiology, and Health Economics at the University of Liège. His research includes cost-effectiveness analyses of prevention and medical interventions related to rheumatic diseases. He also works on methodological subjects in the field, such as modelling techniques and the impact of medication non-adherence on pharmacoeconomic evaluations.

Correspondence: *Mickaël Hiligsmann*, Department of Public Health, Epidemiology and Health Economics, University of Liège, Bât B23, Avenue de l'Hôpital, 4000 Liège, Belgium.
E-mail: m.hiligsmann@ulg.ac.be