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Cost-Effectiveness of Different Strategies for Selecting and Treating Individuals at Increased Risk of Osteoporosis or Osteopenia: A Systematic Review

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A B S T R A C T

Objectives: To compare cost-effectiveness modeling analyses of strategies to prevent osteoporotic and osteopenic fractures either based on fixed thresholds using bone mineral density or based on variable thresholds including bone mineral density and clinical risk factors. **Methods:** A systematic review was performed by using the MEDLINE database and reference lists from previous reviews. On the basis of predefined inclusion/exclusion criteria, we identified relevant studies published since January 2006. Articles included for the review were assessed for their methodological quality and results. **Results:** The literature search resulted in 24 analyses, 14 of them using a fixed-threshold approach and 10 using a variable-threshold approach. On average, 70% of the criteria for methodological quality were fulfilled, but almost half of the analyses did not include medication adherence in the base case. The results of variable-threshold strategies were more homogeneous and showed more favorable incremental cost-effectiveness ratios compared with those based on a fixed threshold with bone mineral density. For analyses with fixed thresholds, incremental cost-effectiveness ratios varied from €80,000 per quality-adjusted life-year in women aged 55 years to cost saving in women aged 80 years. For analyses with variable thresholds, the range was €47,000 to cost savings. **Conclusions:** Risk assessment using variable thresholds appears to be more cost-effective than selecting high-risk individuals by fixed thresholds. Although the overall quality of the studies was fairly good, future economic analyses should further improve their methods, particularly in terms of including more fracture types, incorporating medication adherence, and including or discussing unrelated costs during added life-years.

Keywords: cost-effectiveness analysis, cost-utility analysis, modeling, osteoporosis.

Background

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist [1]. A precursor of osteoporosis is osteopenia in which bone mineral density (BMD) is lower than normal but not yet osteoporotic. Many of these fractures require surgical repair or replacement of the joint. While up to a fifth of patients with osteoporotic fractures of the spine are hospitalized, patients with hip fractures are almost always hospitalized [2]. Because the risk of fracture grows exponentially with age, population aging is expected to increase the socioeconomic burden from osteoporotic fractures in the future. In Germany, for example, total annual expenditures for hip fractures, which were €2.77 billion in 2003, may increase to €3.85 billion in 2030 [3]. For 2050, the projected number of patients with hip fractures is 6.3 million worldwide [2].

Prevention strategies for individuals at increased risk of osteoporotic fractures can be classified into two types: strategies for the period when accelerated bone loss starts, as during perimenopause, immobilization, and corticosteroid use, and strategies for the period when bone loss or fracture has occurred [4]. Although highly effective drug treatments for individuals at increased risk are available, the identification of high-risk individuals is difficult and, as a result, preventive strategies often fail to be cost-effective. In general, identification of high-risk individuals can be based on either a fixed threshold or a variable threshold.

Fixed-threshold analyses

To identify high-risk individuals, in 1994 the World Health Organization (WHO) established a definition of osteoporosis based on BMD. BMD is considered an important predictive factor for osteoporotic fractures and is measured by densitometry [1]. Densitometry results are usually reported as a *T* score, which is the number of SDs between the value of an individual and the mean value of a group of young adults of the same sex [5]. According to the criteria of the WHO, osteoporosis is defined by a *T* score of −2.5 or less and osteopenia by a *T* score of less than −1 and greater than −2.5 SD [1]. Most randomized controlled trials of pharmacological agents to prevent fractures have used dual x-ray absorptiometry (DXA) at the hip or the spine as the preferred method to select high-risk individuals on the basis of BMD. Because treatment of individuals selected by methods other than DXA (e.g., quantitative ultrasound

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[QUS]) may not result in the same risk reduction, DXA has been the most common method used for measuring BMD [6].

There are many other factors besides BMD, however, that determine fracture risk, for example, variability of bone microarchitecture, liability to fall [7], or bone markers (i.e., serum and urine markers of bone turnover) [8]. Because the correlation between BMD in a person today and 15 years or more later is poor [9] and because many fractures occur among persons with normal bone density [10], screen-and-treat strategies based on BMD alone have been either not cost-effective or cost-effective only within certain ranges of drug costs, age, and societal willingness to pay [11]. Therefore, researchers have included several prescreening tools for the measurement of BMD.

Prescreening tools based on clinical risk factors (CRFs) such as prior fracture or low body mass index can be used to estimate a pretest probability of osteoporosis based on DXA as a reference standard. Prescreening tools range from very simple tools such as the Osteoporosis Self Assessment Tool, which is based on age and weight only, to more complex rules with arbitrary scoring systems [12]. When evaluating the cost-effectiveness of several decision rules, the additional costs per case detected of prescreening with a decision rule were much lower than those of extending DXA to all women older than 50 years (€118 vs. €327), even if the most expensive decision rule was used [13].

Using a fixed threshold, selection of individuals depends on the measurement of BMD on the basis of WHO criteria of osteoporosis and osteopenia [1]. For this review, analyses were considered as fixed-threshold analysis if a fixed *T* score was used for selecting individuals at high risk.

Variable-thresholds analyses

Since 2001 several models for calculating fracture risk by including CRFs in the assessment have been further devised and evaluated [14–17]. Researchers were increasingly aware how CRFs are interrelated, and they were able to calculate variable thresholds for risks of fracture. Because these calculations are based on extensive data collection, and because it enables physicians to calculate the risk of an event for both men and women at different ages, this approach is similar to the Framingham cardiovascular risk assessment [7]. By combining several continuous (e.g., age) and dichotomous (e.g., immobility) variables with BMD, the gradient of risk (GR), which is the relative risk of fracture per SD change in BMD [18], increases compared with BMD alone.

The BMD *T* score required to reach a specific risk threshold varies by age, gender, and the presence of additional CRFs. This leads to improved sensitivity with only a moderate loss of specificity [19]. For this reason, the WHO and other organizations recently have recommended using an individual's 10-year risk of fracture to guide treatment decisions [20]. To improve patient assessment at a secondary-care level, an algorithm named the Fracture Risk Assessment Tool (FRAX) was developed by a WHO task force. The CRFs used for the FRAX algorithm can be applied to several countries, and include a parental history of a hip fracture, current smoking, alcohol intake of more than two units daily, rheumatoid arthritis, intake of oral glucocorticoids, and previous fragility fracture [21]. Even CRFs alone may be of diagnostic value for predicting fracture risks because age-specific gradient of risks are similar to those of BMD alone [22]. The National Institute for Health and Clinical Excellence (NICE), however, is skeptical that recommendations about treatment should be based on absolute risk as calculated by using FRAX because not all CRFs included in the WHO algorithm are appropriate (i.e., there is no strong evidence for a treatment effect on fracture risk for risk factors other than low BMD, age, and prior fracture). In addition, absolute fracture risk is not directly related to cost-effectiveness [23]. Hence, the choice of CRFs is still a matter of debate.

By using a variable threshold, the absolute long-term probability of an osteoporotic fracture is estimated on the basis of age, sex, and CRFs, including, but not limited to, BMD [1]. While at younger ages a variable threshold can be reached only with a substantially decreased *T* score, at older ages it can be reached with a moderately decreased *T* score. For this review, analyses were considered as variable-threshold analysis if a variable *T* score was used for selecting individuals at high risk.

For the prevention of fractures, different antiosteoporotic drugs are available. The commonly used drugs are bisphosphonates (e.g., alendronate or risedronate), which inhibit osteoclast-induced bone resorption [24]. Other treatment options include hormone replacement therapy, parathyroid hormone, raloxifene, strontium ranelate, or bazedoxifene. The efficacy of almost all these agents was evaluated on the basis of the WHO threshold of osteoporosis (*T* score <-2.5). Exceptions are clodronate, which also belongs to the group of bisphosphonates, and bazedoxifene, which is a selective estrogen receptor modulator. Both were evaluated in women selected by the FRAX algorithm [25].

Several systematic reviews of cost-effectiveness analyses of osteoporosis screening published until 2006 compared different fixed-threshold strategies, the methods of evaluating these strategies, and the results of these analyses [11,24,26,27]. Based on these reviews, recommendations were made to improve cost-effectiveness modeling; for example, future modeling studies should have a lifelong perspective due to the long-term effects of osteoporosis on costs, mortality, and quality of life, and they should consider case-finding costs. Since 2006 several cost-effectiveness analyses of screen-and-treat strategies for osteoporosis have been conducted, with an increasing number of them based on variable thresholds. Building on previous reviews, the aim of this systematic literature review was to provide an overview of cost-effectiveness modeling analyses for osteoporosis since 2006 and to compare the results of analyses based on a fixed-DXA threshold with those based on variable thresholds for selecting high-risk individuals.

In addition, several methodological aspects of the analyses that were considered as in need of improvement in previous reviews were evaluated [27]. As a result of inconclusive recommendations, the majority of earlier conducted studies did not include a societal perspective, and so important cost items were excluded from the analysis [27]. According to recommendations for health economic evaluations on osteoporosis treatment, a societal perspective should be carried out, which implies that unrelated medical costs and nonmedical costs minus production gains should also be included in added years of life as recommended in guidelines for economic evaluations of interventions in osteoporosis [27–29]. This position is not taken up by NICE, whose position is restricted to costs and cost savings for the National Health Service and personal social services, except for circumstances noted by the Department of Health [30].

Because medication adherence was considered inconsistently in previous analyses [11], our review aimed to evaluate how aspects of adherence were included in more recent analyses. Moreover, the sources of data on utility were of interest because in earlier studies epidemiological data were more accurately referenced to empirical studies than were data on costs and utilities [27].

Methods

Literature search

A literature search in the Medline database was performed to select cost-effectiveness models on screen-and-treat strategies of osteoporosis published from January 2006 to November 2011. Search terms (including MESH terms and text words) were costs and cost analysis, decision making, osteoporosis, densitometry,