Original Article

The Long-Term Effectiveness of Preventive Strategies for Osteoporosis in Postmenopausal Women: A Modeling Approach

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Abstract. Based on data from the literature, we have developed a computer-based simulation model to compare the long-term effectiveness of different preventive strategies of osteoporotic fractures. The Markov model comprises 25 states, including states which describe women distributed according to three levels of fracture risk, fractures states, post-fracture states and a death state. We chose eight standard preventive strategies, which we compare with the ‘No Treatment’ reference strategy. The first two strategies consist in treating all 50-year-old women for 5 or 10 years with hormone replacement therapy (HRT). Strategies 3 and 4 aim at assessing a 5-year course of treatment with bisphosphonates in osteopenic and osteoporotic 65- or 75-year-old women. Strategies 5 and 6 combine 5 years of HRT in all 50-year-old women with 5 years of bisphosphonates in osteopenic and osteoporotic women at 65 or 75 years. The last two strategies simulate 10 years of HRT in all 50-year-old women, followed by strategy 3 or strategy 4. Simulated life expectancy and mean ages of fracture occurrence fit well with the observed data. All the preventive strategies tested reduced the number of fractures. Early 10-year HRT in all women, plus 5 years of bisphosphonates in women at risk of fractures at 65 or 75 years, are the most effective strategies, with an 18.4–19.0% reduction in all fractures, and a 25.6–26.1% reduction in the number of hip fractures. Strategy 2 has a similar outcome, thus demonstrating the value of treatment started early and sustained over a long period. The strategies implemented later, S3 and S4, only concern women at risk (i.e., osteopenic or osteoporotic), and are less effective, with a 1.5–2.1% decrease in all fractures. The combined strategies, S5 and S6, produce intermediate results: a 12.9–13.5% reduction in the number of all fractures and a 17.5–17.9% reduction in hip fractures.

Keywords: Fractures; Modeling; Osteoporosis; Postmenopausal

Introduction

Consensus conferences and a World Health Organization (WHO) working party have defined osteoporosis as a systemic skeletal disease characterized by both low bone mass and microarchitectural deterioration of the bone [1]. The clinical significance of osteoporosis lies in the fractures it occasions, mainly of the hip, the spine and the wrist, although many other bones may be affected [2]. Several prospective studies have shown that there is a gradient of risk between a decrease in bone mineral density (BMD) and an increase in the incidence of fractures. In 50-year-old Caucasian women, the lifetime risk is estimated at about 15% for hip fracture and about 45% for all osteoporotic fractures [3]. Incidence rates of osteoporotic fractures are expected to rise dramatically over the decades to come, mainly because of demographic changes [4]. Given the cost of osteoporotic fractures (especially hip fractures), and other consequences in terms of mortality, disability, loss of autonomy and quality of life, preventive strategies are clearly required. Hormone replacement therapy (HRT) [5,6] and bisphosphonates [7,8] have, in observational
and experimental studies, demonstrated their ability to reduce the incidence of osteoporotic fractures in postmenopausal women, because of their positive effects on bone remodeling and bone density.

However, these studies, which have mainly been conducted in the context of drug registrations, are of limited value from a more general public health point of view. They tend to compare a specific product with a placebo and not specific products with each other. They test individual products rather than true therapeutic strategies, a strategy being defined as the combination of a treatment, an age of initiation and a duration. A distinction should also be made between a pure strategy (one product, one age, one duration) and mixed strategies, which combine different products given at different ages during different periods of time. Finally, and most important, observational studies are generally conducted in a short-term perspective, whereas the full benefit of preventive strategies can only be assessed in the long term. Moreover, it is a controversial issue to know whether the treatment effect, whatever this is, is permanent or transitory. Recent studies have suggested a ‘catch-up’ effect, meaning that the BMD of treated women resumes its former trend once treatment has been terminated [9]. However, the speed of the effect remains unclear, in spite of being of crucial importance: the average age of women with hip fractures in France is over 80 years, while HRT is generally initiated at the menopause, that is at around 50 years of age.

The use of modeling techniques cannot thus be avoided if we are to try to measure and compare the long-term effectiveness of different preventive strategies on osteoporotic fractures and life expectancy in postmenopausal women. We present here such a model, based on epidemiologic and efficacy data drawn from the literature, which retraces the natural history of osteoporosis and simulates the effects on health of different preventive strategies.

Materials and Methods

Overview of the Model

We developed a Markov model, which enables simulation of the follow-up of a defined population over time. At each period, ‘transition probabilities’ allow patients to move stochastically from one health state to another. The model permits computation of statistics such as life expectancy, or average time spent in a definite health state. This well-known technique is widely used for the evaluation of medical treatments [10], especially when observational data are missing. Our model simulates the time-life gradual changes in women health status over the age of 50 years. At each time period, the population is divided into different categories corresponding to the different levels of fracture risk, i.e., normal, osteopenic or osteoporotic.

At each time period, surviving women can experience events such as fractures or death. The output of the model is therefore:

- life expectancy
- number of hip, vertebral and wrist fractures at each age
- average number of each type of fracture over a lifetime
- the number of women requiring treatment

Model Health States

The model includes (1) ‘pre-fracture’ states, describing the distribution of women according to the three levels of fracture risk (‘normal’, ‘osteopenic’, ‘osteoporotic’), (2) ‘fracture’ states (first fracture or recurrence) including three types of fracture (hip, vertebral or wrist fracture), (3) ‘post-fracture’ states, describing gradual changes in patients following their fracture, and (4) a ‘death’ state. We assume that at each stage bone loss is distributed normally. Definitions of ‘pre-fracture’ states are based on the WHO Working Group guidelines [11], osteoporosis being defined as a BMD more than –2.5 standard deviations (SD) below the average BMD in a young adult population ($T$-score ≤ –2.5), and osteopenia as a BMD between –1 SD and –2.5 SD below the reference value ($–2.5 < T < –1$). Normal BMD is above or equal to –1 SD the reference average in young adults. Finally, 25 health states are defined and listed in Table 1. They fall into one of the following categories:

- ‘stable states’ in which transition to another state can occur at any moment (states 1 to 6 and 24 to 25);
- ‘transient states’, in which women can stay for only one time period (i.e., 6 months) before moving to another state. These states represent ‘events’ (states 7 to 22) such as fractures;
- ‘absorbing state’ where no transition to any other state is allowed. The ‘death’ state is obviously such a state.

Fracture states are transient states which describe the immediate (6-month) consequences of a fracture (hospitalization, surgery, etc.). Surviving patients can neither remain in these transient states nor move back to their initial state. They can jump to one of the ‘post-fracture’ states characterized, in some cases, by the institutionalization of the patient, or eventually to the ‘death’ state.

Each of these situations can have various results: stability, aggravation, recurrence or death. Recurrence of hip fracture is not considered in our model, since we consider the goal of preventive treatment is mainly to avoid the first hip fracture episode. Recurrence of other fracture types is possible.

The model cycles are 6 months long. Considering the mean time of hospitalization for a hip fracture (23 days) and the convalescence period required, 6 months seems to constitute a reasonable period to assess the outcome of a fracture (death, recovery and return home, institutionalization, etc.).