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Managing osteoporosis with FRAX® in Australia: Proposed new treatment thresholds from the 45&Up Study cohort

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ABSTRACT

Introduction: Many people at high risk of fractures are not following traditional guidelines and not being recommended for intervention. This study aimed to propose and evaluate a new set of intervention thresholds.
Methods: Participants were 213,375 men and women aged ≥50 years living in New South Wales, Australia. Fracture Risk Assessment Paper Charts (Australia) was used to estimate the 10-year fracture risk. The standardized rates (to Australia population distribution 2007) for intervention were calculated for different thresholds: our proposed new thresholds (i.e. 10-year probability of hip fracture: ≥3%, 5% or 7% for 50–69, 70–79 and ≥80 years respectively), thresholds by the National Osteoporosis Guideline Group (NOGG) approach, UK thresholds and US thresholds.
Results: The NOGG, UK and US thresholds did not work well in the Australian population. For example, the NOGG and UK thresholds respectively qualified only 1 in 12 (8.1%) and 1 in 9 (11.3%) Australian men aged ≥70 years and the US thresholds qualified about 9 in 10 (90.6%) Australian women aged ≥70 years. For men or women aged ≥70 years, our proposed new thresholds gave more realistic treatment rates of 21.6% for men and 70.5% for women. Compared to the current Australian guidelines (i.e. T-score ≤ −2.5 and age ≥ 70 years or a fragility fracture), our thresholds identified an additional 4.9% of men and 18.2% of women aged ≥ 70 years for treatment.
Conclusion: The proposed new thresholds could identify currently under-recognised high-risk individuals for treatment. It should be considered as a recommendation for osteoporosis management in Australia.

Introduction

Risk-based strategies for osteoporosis management have been advocated especially after the introduction of the Fracture Risk Assessment Tool (FRAX®) by the World Health Organization in 2008 [1–3]. In many countries including Australia, the 10-year probability of hip or major osteoporotic fracture can now be estimated using clinical risk factors with or without bone mineral density (BMD) results [4]. With about one in two low-trauma fractures occurring in persons without osteoporosis (i.e. BMD T-score > −2.5) [5], it is important to identify osteopenic individuals who are at high risk of fractures. Also, osteoporotic individuals without a prior fracture may live in areas where BMD testing is not available. These high-risk persons are likely to benefit most from osteoporosis pharmacologic therapy but are not recommended for treatment according to the traditional guidelines (e.g. T-score ≤ −2.5 and age ≥ 70 years or a fragility fracture [6]). They should be identified and have the opportunity to become candidates for intervention.

There is no universally accepted fracture risk level for osteoporosis pharmacologic therapy [7–10]. Intervention thresholds with FRAX vary from country to country due to not only different approaches used in setting the thresholds [11–13] but also differences in the risks of fracture and death between countries [14]. In addition, appropriate intervention thresholds depend critically on country-level factors such as reimbursement issues, cost-effectiveness of the pharmacologic therapy and the society's willingness to pay for health care of osteoporosis [15].

In 2008, the US National Osteoporosis Foundation recommended the initiation of pharmacologic therapy for osteoporosis in postmenopausal women and men aged 50 and older with osteopenia (−2.5 < T-score ≤ −1.5) if the 10-year probability of any major osteoporotic fracture is ≥20% or of having a hip fracture is ≥3% [16]. An economic analysis showed that pharmacologic therapy for osteoporosis is cost-effective at these recommended thresholds [9]. In other countries such as UK and France [11,12], age-specific intervention thresholds for both men and women are set to the corresponding fracture risk level equivalent to that of a same-age women who has had a prior fracture.

In Australia, pharmacologic therapy for osteoporosis is subsidised by government under the following conditions: (1) a fragility fracture,

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(2) age ≥ 70 years and T-score ≤ −2.5 or (3) receiving 7.5 mg prednisone or equivalent for more than three months and have a T-score ≤ −1.5 [17]. These criteria are not directly related to a person's absolute risk and currently no reimbursement is based on the absolute fracture risk calculations despite the growing use of these estimates in clinical consultations. As a result, a good balance between burdens of osteoporotic fractures and benefits of pharmacologic therapy may not be achieved. Clearly, fracture risk levels for subsidised pharmacologic therapy needs to be considered in Australia, as well as the impact of implementing risk-based strategies for osteoporosis management.

The aims of this study are to (1) describe proportions of Australian men and women aged 50 years and older who are at high risk of osteoporotic fractures according to different fracture risk cut-offs, (2) determine appropriate fracture risk thresholds for the initiation of pharmacologic therapy for osteoporosis in Australia, and (3) report current osteoporosis management patterns among selected high-risk persons in a large cohort study of older Australians (the Sax Institute's 45&Up Study [18]).

Methods

Study population

The study subjects are 213,375 (102,590 males and 110,785 females) participants from the 45&Up Study (total number of participants 267,153). This study excludes participants who were aged <50 years, had missing body mass index (BMI) data, or were on anti-resorptive therapies for non-osteoporosis diseases. The study was approved by the NSW Population and Health Services Research Ethics Committee (Approval no. 2012/06/396). The 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee.

Data sources

The 45&Up Study is a large cohort study which recruited about one in 10 men and women aged 45 years and older during 2006 to 2009 in New South Wales (NSW), Australia. With about one third of the Australian population living in NSW, it is the largest state in the country. The study is described in detail elsewhere [18]. In brief, the 45&Up Study randomly selected participants from the database of Australia's universal health insurance provider (Medicare Australia) which covers virtually the entire population. The study oversampled residents aged 80 years and older and residents in rural areas by a factor of two and all residents in remote areas. It had an overall response rate of 18%. Eligible individuals took part in the study by completing a self-administered postal questionnaire about their background, lifestyle, health and health service use and giving signed consent for participation and follow-up, including linkage to a range of health databases.

Health care information in connection with claims under the Pharmaceutical Benefits Scheme (PBS) and the Medicare Benefits Scheme (MBS) are collected by Medicare Australia [19]. The PBS dataset covers all government-subsidised claims for prescribed medicines and contains information such as PBS item number (coded to the Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners), date of supply, number of scripts filled for each PBS item per patient per date of supply, type of prescription (original, repeat, etc), payment category (general, concession card, pensioner, repatriation, safety net, etc) and demographic data. The MBS dataset includes all claims for medical services with MBS item numbers for which a government subsidy was paid.

The baseline questionnaire data of the 45&Up Study have been linked to PBS and MBS datasets using an encrypted version of the unique Medicare ID. Only de-identified data are made available to researchers.

Fracture risk calculation

The Fracture Risk Assessment Paper Charts (Australia), FRAX, was used to estimate mean fracture risk based on gender, age, BMI, and a number of other clinical risk factors [4]. The risk estimations in the charts are for every 5-year increment in age. We estimated fracture risk for each year increment in age, by dividing the difference between two adjoining 5-year increment estimations (the current one and next adjoining one) by 5. The FRAX® tool, which was developed from population-based cohorts from Europe, North America, Asia, and Australia, is based on individual patient models which integrate the risks associated with clinical risk factors and BMI. The algorithms are based on the hazard functions for fractures and for death in a specific country and are used to compute the 10-year probability of hip fracture and/or major osteoporotic fractures (hip, clinical spine, forearm or proximal humeral fracture) from the time of assessment.

The risk factors for the risk calculation in this study include fracture in the previous five years, parental fractured hip, current smoking, alcohol use (≥3 units/day), rheumatoid arthritis (i.e. ever use of biologic disease-modifying anti-rheumatic drugs in PBS dataset), secondary osteoporosis (i.e. type I diabetes or premature menopause <45 years) and use of glucocorticoids. Type I diabetes is defined as reporting diabetes in the questionnaire (i.e. Has a doctor EVER told you that you have diabetes?) with PBS evidence of insulin injection use, and glucocorticoid use is defined as current use or has been used for more than 3 months at a dose of 5 mg prednisolone daily or more (or equivalent doses of other glucocorticoids).

Use of pharmacologic therapy and BMD testing

Information on use of osteoporosis pharmacologic therapy (i.e. anti-resorptive agent or teriparatide) for osteoporosis and BMD testing are ascertained from the PBS and MBS datasets. In Australia, anti-resorptive drugs (e.g. alendronate, risedronate, zoledronate, raloxifene, strontium ranelate or denosumab) and teriparatide are subsidised for osteoporosis by the government. It is therefore very unlikely that patients with osteoporosis would use drugs other than the subsidised ones. For example, fewer than 1% of patients who had the BMD test in our large clinical department in the last five years were not entitled to the government subsidy. Bone densitometry for BMD is also provided via Medicare at a subsidised rate for both men and women with a fragility fracture, or aged 70 years or over, known hypogonadism, chronic glucocorticosteroid use, chronic liver & renal disease, hyperparathyroidism & hyperthyroidism, rheumatoid arthritis and malabsorption [20].

Statistical analysis

The proportions of participants with each fracture risk factor were presented by age and gender. We calculated 10-year probabilities of hip fracture and of major osteoporotic fractures for all participants according to their risk factor profile at the baseline survey. For participants with a prior fracture, mean fracture risk was estimated for each five-year age group by gender. Since physicians would not usually investigate persons without fracture risk factors, and persons with a prior fracture are already recommended for treatment, only participants with a fracture risk factor other than prior fracture were considered further. They were divided into high or low risk according to different cut-offs and the proportions were reported and evaluated. The results were then used to determine appropriate risk thresholds for treatment.

We calculated proportions of participants who would qualify for pharmacologic treatment according to our proposed new thresholds, thresholds by the National Osteoporosis Guideline Group (NOGG) approach [15] (see Table 4 for details), and the recommended thresholds of the US (i.e. 10-year probability of hip (or major osteoporotic) fracture: ≥3% (or 20%) for ≥50 years) [13] and the UK (i.e. 10-year probability of hip (or major osteoporotic) fracture: ≥1.0% (or 7.5%) for 50–54 years,