When the FRAX® test is applied to controlled clinical trials

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Summary

FRAX® is a computer-based algorithm developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases in Sheffield (UK). This algorithm calculates fracture probability from easily obtained clinical risk factors in men and women: age, sex, body mass index and dichotomized variables comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, use of long-term oral glucocorticoid, rheumatoid arthritis, other causes of secondary osteoporosis and high alcohol consumption (femoral neck bone mineral density can be optionally input to enhance fracture risk prediction). The output of FRAX® is the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture.
Recently various Authors have re-evaluated the effectiveness of drugs approved for postmenopausal osteoporosis to test whether they are more effective in women with higher FRAX® probabilities.

KEY WORDS: FRAX®; alendronate; clodronate; strontium ranelate; raloxifene; bazedoxifene; denosumab.

Introduction

Osteoporosis is a major public health problem, affecting millions of people worldwide. It is operationally defined on the basis of bone mineral density (BMD) assessment and according to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <-2.5 SD) (1). This criterion has been widely accepted and, in many countries, provides both a diagnostic and intervention threshold.
In the past decade, a great deal of research has taken place to identify factors other than BMD that contribute to fracture risk, for example: age, sex, the degree of bone turnover, a prior fracture, a family history of fracture, and lifestyle risk factors such as physical inactivity and smoking. Some of these risk factors are partially or wholly independent of BMD and could, therefore, enhance the information provided by BMD alone. For these reasons, WHO approved a program of work at the WHO Collaborating Centre at Sheffield to identify and validate clinical risk factors for use in fracture risk assessment alone or in combination with bone mineral densitometries and to develop an algorithm for risk assessment to be used in the context of many primary care settings, also when BMD testing was not available (2).
On this basis was elaborated the FRAX®, a computer-based algorithm (available at www.shef.ac.uk/FRAX), that provides the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) both in men and women. The risk of fracture is calculated from age, BMI computed from height and weight, and dichotomized risk variables comprising: prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever long-term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and daily alcohol consumption of three or more units daily. Additionally, femoral neck BMD can be entered, preferably as a T-score. The performances of FRAX® were evaluated in 11 independent cohorts that did not participate in the model synthesis, though further validation is required in men and in particular ethnic groups (3, 4).
The identification of individuals at high risk for osteoporotic fractures is an important principle in the delivery of health care to those most at need, particularly where health care resources are limited. Indeed the European regulatory agency (CHMP) has revised its guidelines for the development of agents in the treatment of primary osteoporosis (5) to take account of this principle, considering the 10-year probability of fracture, in line with the recommendations of the WHO (2).
Recently various Authors, above all the group of Sheffield headed by John Kanis, have re-evaluated the effectiveness of drugs approved for postmenopausal osteoporosis to test whether they are more effective in women with higher FRAX® probabilities. Up to now, the analyses about clodronate, alendronate, raloxifene, bazedoxifene, strontium ranelate and denosumab are available in form of published study or abstract presented to a world meeting (Table 1).

Clodronate

McCloskey et al. (6) evaluated the effect of clodronate (a non-nitrogen-containing bisphosphonate) studying a cohort comprising 3,974 out of 5,212 women (76.2%), recruited to the main part of the study in whom complete data on clinical risk factors required for the computation of 10-year fracture probability were available. The original study was a double-blind, prospective, randomized, placebo-controlled study in elderly community-dwelling women aged 75 years or more. Following randomization, the women received either clodronate 800 mg daily or an identical placebo. The interaction between fracture probability, calculated using the FRAX® and treatment efficacy, examined by Poisson regression, was significant when probability was assessed without BMD (p=0.043), but not when BMD was included (p=0.10). Efficacy was more evident in those deemed at highest risk.

Alendronate

An analysis of the interaction between alendronate (a nitrogen-containing bisphosphonate) efficacy and baseline FRAX® probabilities in the clinical fracture arm of the FIT has been presented at the ASBMR Congress in Denver (2009) (7).The authors did not find any significant association between FRAX® probability, calculated with femoral neck BMD, and reduction in risk of clinical or nonvertebral fractures by alendronate. Results were similar for "major osteoporotic fractures" and whether or not FRAX® calculations included femoral neck BMD. The authors concluded that there is no significant association between FRAX® score and efficacy of alendronate for nonvertebral or major clinical fractures.

Raloxifene

The Multiple Outcomes of Raloxifene Evaluation (MORE) study showed that the raloxifene, a selective estrogen receptor modulator (SERM), at the dosage of 60 mg daily, has a significant effect on vertebral fracture risk and no significant effect on non-vertebral fractures (8). A post hoc analysis in patients with moderate or severe vertebral fractures at baseline has shown that, in this subgroup of patients at high risk, raloxifene treatment was associated with a significant decrease in non-vertebral fracture (9). Such data suggested that raloxifene might have effects on non-vertebral fracture risk in women with high fracture probabilities at entry to the MORE study. For this reason, Kanis et al. (10), tested whether the efficacy of raloxifene varied according to baseline fracture probability estimated using FRAX®. Contrary to expectation, the authors observed that the effectiveness of raloxifene for clinical and morphometric fracture is comparable over the whole range of FRAX® probabilities and the interaction between fracture probability and treatment was not significant.

Bazedoxifene

Bazedoxifene is a new SERM, that both at the dosage of 20 and 40 mg daily, showed a significant effect on vertebral fracture risk but similarly to the raloxifene without significant effect on non-vertebral fractures. A post hoc analysis in a subgroup of patients at high risk (femoral neck T-score ≤–3 SD and or ≥1 moderate or severe, or multiple mild vertebral fractures) reported that bazedoxifene 20 mg daily reduced the incidence of non-vertebral fractures by 50% compared to placebo. The effect of the higher dose was not significant (11). Kanis et al. (12) re-evaluated the efficacy of bazedoxifene on fracture outcomes avoiding subgroup analysis by examining the efficacy of intervention as a function of fracture risk evaluated by FRAX®. The interaction term between baseline FRAX® score and effect of treatment on fracture outcomes was not significant ($p>0.3$) but, for both all clinical and morphometric vertebral fractures, the hazard ratio fell progressively with increasing baseline fracture probability. The effects of bazedoxifene on morphometric and any clinical fracture were significant in patients with fracture probabilities above the 25th and 75th percentile respectively.

Strontium ranelate

Strontium ranelate is a member of a new family of drugs for the treatment of osteoporosis, named DABAs (dual action bone agents) for their capacity to uncouple bone turnover increasing bone formation and reducing bone resorption (13). A large placebo-controlled phase III trial, the SOTI (Spinal Osteoporosis Therapeutic Intervention) study (14), showed that strontium ranelate decreased the risk of vertebral fracture with no significant effect on non-vertebral fracture. Afterwards the TROPOS (Treatment of Peripheral Osteoporosis) study (15) also showed a decreased risk of vertebral fracture and a significant effect on non-vertebral fracture after 3 and 5 years of treatment. In the same study, a reduction in hip fracture rates was reported in a post hoc subgroup analysis in patients considered to be at high risk. Kanis et al. (16) aimed to explore the effects of strontium ranelate on clinical fractures and on morphometric vertebral fractures in relation to baseline fracture probability estimates using FRAX®. Similarly to the recent paper about raloxifene (10), the authors showed no evidence of a significant interaction of fracture probability with efficacy. The finding was similar with the addition or absence of BMD in the FRAX® model. Therefore strontium ranelate exhibited an anti-fracture efficacy the entire range of FRAX® probabilities.

Denosumab

Denosumab, a fully human monoclonal antibody, binds to receptor activator of NF-kB ligand (RANKL) and blocks stimulation of RANK, thus inhibiting osteoclast development, activity and survival. The Freedom trial, a large phase 3 study conducted in postmenopausal women with osteoporosis, demonstrated that subcutaneous administration of 60mg of denosumab, every 6 months, decreased the risk of new vertebral and hip fractures by 68% and 40%, respectively (17).
Very recently, McCloskey et al., re-evaluating the effects of denosumab, reported that its efficacy was greater in postmenopausal women at moderate to high risk of fracture as assessed by FRAX® (18).

Conclusions

The studies reviewed here are at the moment the only contributes that analyze the effects of agents approved for the treatment of osteoporosis in function of the baseline FRAX® probabilities. The results are conflicting, while in fact the action of clodronate, bazedoxifene and denosumab seems to be better in patients who present higher risk at the baseline, these evidences lack for strontium ranelate, alendronate and raloxifene.
Differently from the post hoc analysis, the examination of the interaction of treatment efficacy with baseline FRAX® probabilities, while not avoiding post hoc status, aims to avoid subgroup analysis and the associated loss of statistical power.
Probably, other studies that analyze the interaction between treatment efficacy and baseline FRAX® probabilities will shortly be published, but above all the new trials would have to be designed at the beginning considering the baseline risk of fracture.

Table 1 - Effect of treatments for osteoporosis in function of FRAX® probabilities.

Drug	Effect in function of FRAX® probabilities	References
Clodronate	Yes, better in patients at high risk	6
Alendronate	No	7
Raloxifene	No	10
Bazedoxifene	Yes, better in patients at high risk	12
Strontium ranelate	No	16
Denosumab	Yes, better in patients at moderate-high risk	18

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