Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. ■, no. ■, 1–7, 2017

1094-6950/■:1–7/$36.00
http://dx.doi.org/10.1016/j.jocd.2017.06.013

Original Article

Overview of Fracture Prediction Tools

John A. Kanis,[*,1,2,3] *Nicholas C. Harvey,*[4] *Helena Johansson,*[1,4] *Anders Odén,*[1] *Eugene V. McCloskey,*[1] *and William D. Leslie*[5]

[1]*Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK;* [2]*Institute of Health and Ageing, Australian Catholic University, Melbourne, Australia;* [3]*MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK;* [4]*Centre for Bone and Arthritis Research (CBAR), Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and* [5]*Department of Internal Medicine, University of Manitoba, Winnipeg, Canada*

Abstract

The characterization of risk factors for fracture that contribute significantly to fracture risk, over and above that provided by the bone mineral density, has stimulated the development of risk assessment tools. The more adequately evaluated tools, all available online, include the FRAX® tool, the Garvan fracture risk calculator and, in the United Kingdom only, QFracture®. Differences in the input variables, output, and model construct give rise to marked differences in the computed risks from each calculator. Reasons for the differences include the derivation of fracture probability (FRAX) rather than incidence (Garvan and QFracture), limited calibration (Garvan), and inappropriate source information (QFracture). These differences need to be taken into account in the evaluation of assessment guidelines.

Key Words: Calibration; fracture risk; FRAX; Garvan fracture risk calculator; QFracture.

Introduction

A significant advance over the past 15 yr has been the development of medical interventions that have been shown in high-quality randomized controlled trials to decrease the risk of fragility fractures *(1,2)*. Unfortunately, a minority of men and women receive treatment even after sustaining a fragility fracture *(1,3)*. The reason for a large treatment gap (the difference between the number of individuals at high risk and the proportion of the population that receives treatment) is complex and multifactorial. However, one of the reasons is limitations in the assessment of fracture risk.

Although the diagnosis of the disease relies on the quantitative assessment of bone mineral density (BMD), a major determinant of bone strength, the clinical significance of osteoporosis lies in the fractures that arise. The causation of fractures is, however, multifactorial. In this respect, there are some analogies with other multifactorial chronic diseases. For example, hypertension is diagnosed on the basis of blood pressure, whereas an important clinical consequence of hypertension is stroke, the likelihood of which is dependent on multiple factors including hypertension.

Despite many guidelines using BMD thresholds to determine whether treatments should be recommended, the multifactorial nature of fracture risk means that BMD does not capture nonskeletal determinants of fracture risk, such as liability to fall. A number of risk factors for fracture has been identified that contribute significantly to fracture risk over and above that provided by BMD *(4)*. A good example

Conflicts of interest: Professor Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases; he has no financial interest in FRAX. Professors McCloskey, Oden, Harvey, and Dr. Johansson are members of the FRAX team. Professors Kanis, Harvey, and McCloskey are members of the advisory body the National Osteoporosis Guideline Group. Professor Leslie led the team that developed the Canadian FRAX tool and co-led the Osteoporosis Canada guidelines that endorsed the use of FRAX.

Some content in this review is taken from Kanis JA, et al (2016) Calcif Tissue Int 98: 417-25 with kind permission from Springer Science+Business Media B.V.

*Address correspondence to: John A. Kanis, MD, Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK. E-mail: w.j.pontefract@shef.ac.uk

is age, where the same BMD has a different significance at different ages, such that fracture risk is much higher in the elderly than in the young *(5,6)*. This is because age contributes to risk independent of BMD. The realization that independent risk factors in combination with BMD predict fractures with greater accuracy than BMD alone *(4)* has led to the development of risk prediction tools to better categorize individuals at high or low risk and, in turn, to optimize clinical decision making with regard to therapeutic intervention. This paper reviews the strengths and weaknesses of the most commonly espoused risk assessment tools.

Fracture Risk Prediction Tools

Several assessment tools have been derived, most of which have been poorly validated *(7,8)*. The more adequately evaluated tools, all available online, include the FRAX® tool *(7)*, the Garvan fracture risk calculator *(9,10)*, and, in the United Kingdom, the QFracture® *(11,12)*.

FRAX

The FRAX algorithm is based on a series of meta-analyses of data from 12 independent fracture studies from North America, Europe, Asia, and Australia *(13–18)*, which comprised a total of 60,000 men and women with more than 250,000 person-yr of follow-up and included more than 1100 cases of hip fracture and 3300 osteoporotic fractures *(7)*.

After the fracture risk algorithm had been constructed using primary data from these studies, a validation study was performed using individual-level data from 11 independent population-based cohorts that were not used in the development of the original model *(19)*. The latter comprised a total of 230,000 individuals with more than 1.2 million person-yr of follow up. By reason of its large numbers, its international character, and the care taken in its construction and implementation, the FRAX algorithm is considered to have unique authority *(20)*. The algorithm provides information on the 10-yr probabilities of hip fracture and any major osteoporotic fracture (defined as a hip, wrist, humerus, or clinical vertebral fracture). Further details are provided in an accompanying paper in this volume.

QFracture

The QFracture tool is based on a UK prospective open cohort study of routinely collected data from 357 general practices on over 2 million men and women aged 30–85 yr (www.qfracture.org) *(11)*. Like the FRAX tool, QFracture takes into account history of smoking, alcohol and corticosteroid use, parental history (of hip fracture or osteoporosis), and several secondary causes of osteoporosis. Unlike FRAX, QFracture also includes a history of falls (yes or no only over an unspecified time frame) and utilizes a large number of clinical risk factors, and no provision is made for BMD. It has been internally validated (i.e., from a stratum of the same population) and externally validated in a similar population (routinely collected data in general practitioner records). The performance characteristics and calibration in the United Kingdom have been compared with FRAX with comparable results for hip fracture. The tool is not calibrated to the epidemiology of other countries. A feature of QFracture is that it is more cumbersome (more questions) and does not accommodate the inclusion of BMD. BMD measurements are dismissed as "expensive and inconvenient tests" *(11)*, and so the model ignores a wealth of data demonstrating the utility of BMD testing in fracture risk assessment.

Garvan

The Garvan tool (www.garvan.org.au) is based on many fewer men and women from a single study, the Australian Dubbo Osteoporosis Epidemiology Study (DOES) f approximately 2500 men and women 60 yr of age or more. Garvan differs from FRAX by including a history of falls (categorized as 0, 1, 2, and >2 in the previous year) and the number of previous fragility fractures (categorized as 0, 1, 2, and >2), but does not include other FRAX variables such as parental history of hip fracture, secondary osteoporosis, rheumatoid arthritis, glucocorticoid use, smoking, and intake of alcohol. The output of the tool differs from FRAX in that it reports the risk of a larger number of fracture sites (additionally includes fractures of the distal femur, proximal tibia/fibula, distal tibia/fibula, patella, pelvis, ribs sternum, hands, and feet excluding digits). Further details are provided in an accompanying paper in this volume.

Comparative Features

There are important differences in the input variables, output, and model features that make comparison of the models problematic. A summary of input variables is given in Table 1.

With regard to input variables, both Garvan and QFracture include a history of falls, whereas this is not an input variable in FRAX. Indeed the Garvan tool weights the number of falls in the past year. Whereas falls are a strong risk factor for fracture, the incorporation of falls into FRAX is problematic for several reasons. First, at the time of the release of FRAX, existing falls data were not of adequate quality, including the heterogeneous construct of questions on falls. Second, falls risk is inherently taken into account in the algorithm, though not as an input variable. Thus, the fracture probability given for any combination of risk factors assumes that the falls risk is that observed (but not documented) in the cohorts used to construct FRAX. Third, the interrelationship of falls risk with the other FRAX variables has been inadequately explored on an international basis. Fourth, the relationship between the risk variable and mortality needs to be accounted for, but there are no data available.

These technical problems aside, risk assessment tools are intended to identify a risk that is amenable to a therapeutic intervention. However, falls as a risk variable do not