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EDITORIAL

Calibration of FRAX: A Journey, not a Destination

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The management of osteoporosis has been revolutionized by the shift, in part or in whole, from treatment of individuals with low bone mineral density (BMD) T-scores to those with elevated absolute fracture risk based upon clinical prediction tools. Among the available validated tools, FRAX^R is unique in several respects including its ability to customize predictions to a specific target population [1]. This process, known as calibration, ensures that the output from FRAX—10-year probability of major osteoporotic fracture (MOF, a composite of hip, clinical vertebral, proximal humerus, distal forearm) and 10-year probability of hip fracture alone—agrees with the expected fracture risk. This has allowed for the creation of more than 80 FRAX tools covering over 80% percent of the world population. [2] The flexibility of this approach, which recognizes diversity in fracture risk between populations rather than making the flawed assumption that "one size fits all", comes at a price. That price is the need to acquire high quality fracture incidence rates. (Mortality data are also required to incorporate competing mortality into the calculation but are usually easier to obtain.).

Accurate calibration of the FRAX tool is of critical importance. Treatment qualification based upon a fixed 10-year MOF probability threshold of 20% shows a very steep gradient: for every 1% change in calibration, there is a 2.5% change in treatment rates for women and a 4.1% change in treatment rates for men [3]. Therefore, miscalibration of greater than 10–20% can lead to profound over- or under-treatment. Of note, similar levels of miscalibration would be expected to have little if any effect on treatment rates using an age-dependent intervention threshold since the cutoff scales in relation to the tool's predictions [4].

It is self-evident that better quality fracture data will provide more accurate predictions from the derived FRAX tool. Therefore, calibration should ideally be based upon nationwide fracture data. For hip fractures, which almost invariably lead to hospitalization and surgery, many countries are able to provide accurate statistics. Non-hip fractures, which frequently do not require hospitalization or surgery, are more difficult to measure. Clinical vertebral fractures, which may present insidiously rather than acutely, are the most difficult to accurately count. A majority of countries that have a FRAX model do not have robust information on the risk of other major osteoporotic fractures [5]. In the absence of such information, FRAX models often assume that the age- and sex-specific pattern of these fractures is similar to that observed in Malmo, Sweden [6, 7]. This is supported by the observation that in those regions where hip fracture rates are high, so too is the risk of non-hip fractures including forearm fracture and spine fractures (requiring hospital admission) [8–10]. This assumption has also been tested prospectively in Iceland and Moldova [11, 12]. An exception to this generalisation has been reported in two regional fracture surveys in Russia where the incidences of both forearm and humeral fractures were substantially higher than would be predicted from the incidence of hip fracture when comparing with Malmo [13]. Intermediate results have been reported in a population-based study of 21,850 MOF from Canada, where forearm/hip ratios were 35–46% higher and humerus/hip ratios 15–19% higher than in Malmo, although there was excellent agreement in clinical vertebral/hip ratios [14].

Therefore, there is evidence that fracture ratios from Sweden reflect patterns observed in many but not all countries [13–18], despite marked geographic differences in fracture incidence [10]. An illustration of these principles is provided in Fig. 1, which shows ratios of MOF to hip fracture probability obtained from the FRAX website for selected countries based upon whether MOF calibration included data

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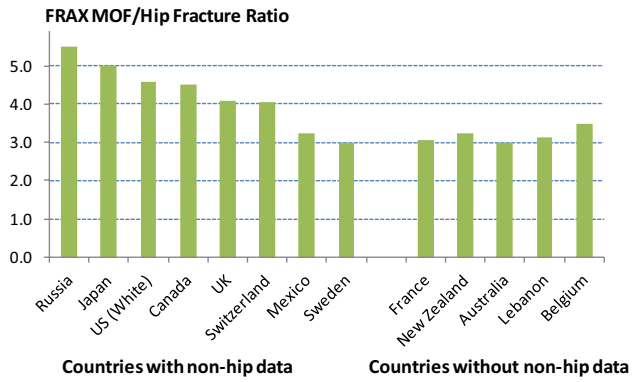

Fig. 1 Ratio of FRAX 10-year major osteoporotic fracture (MOF) to hip fracture probability for selected tools (FRAX Web Version 4.2) based upon whether calibration included data on non-hip fractures (left) or relied on non-hip rates estimated from Swedish databases (right). Ratios are for a woman age 65 years with body mass index 25 kg/m^2, prior fracture and femoral neck T-score − 2.5

on non-hip fractures or relied on rates estimated from the Swedish databases. For some countries with non-hip major fracture data, these ratios are higher than in Sweden while for Mexico the ratio is quite similar to Sweden. Had the Swedish fracture ratios been used, rather than national data, treatment rates (assuming a fixed 10-year MOF probability threshold of 20%) would be projected to decrease by tenfold in Russia and by almost threefold in Switzerland [3]. This highlights the importance of identifying and accommodating regional differences.

In this context, the recent report from Mugisha et al. [19] provides information on calibration of the FRAX tool for Belgium which used Swedish data for estimating non-hip fractures. The population-based FRISBEE cohort registered 1336 fractures in 3560 women over mean 9.1 years of follow-up. Importantly, fractures were validated by radiological/surgical reports and included a credible number of clinical vertebral fractures. The authors found that the ratio of MOF to hip fractures in their population was substantially greater than those reported from the Swedish databases for each of the reported age groups (60–69, 70–79, 80–89 years). Of course, caution needs to be exercised before applying these data clinically since they arise from a single, relatively small cohort, and therefore the generalisability are uncertain and the confidence intervals are very wide. Nonetheless, if these data are confirmed to accurately reflect patterns in the Belgian population then it might justify recalibration of the FRAX tool for Belgium.

In summary, FRAX is a flexible platform for fracture risk prediction that can accommodate between and within country differences in fracture epidemiology. A strength of FRAX is the ability to update predictions and ensure that these remain aligned with the target population despite demographic and temporal changes [20]. The corollary of these findings is that the job is not over after the creation of a FRAX tool. Where adequately powered, high quality data confirm a mismatch between FRAX predicted and observed fracture risk, this may call for updating the FRAX tool. There is precedent for such updates in the lifetime of FRAX (e.g., United States, Turkey, Italy). Periodically evaluating performance of a FRAX tool and making modifications, where justified, will continue to ensure that FRAX advances the management of osteoporosis in patients worldwide.

Disclosures

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