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The utility of absolute risk prediction using FRAX® and Garvan Fracture Risk Calculator in daily practice

Tineke A.C.M. van Geel[a,*], John A. Eisman[b,c,d,1], Piet P. Geusens[e,f], Joop P.W. van den Bergh[f,g,h], Jacqueline R. Center[b,c], Geert-Jan Dinant[i]

[a] Maastricht University/CAPHRI and NUTRIM, Department of Family Medicine, PO Box 616, 6200 MD Maastricht, The Netherlands
[b] Garvan Institute of Medical Research, Osteoporosis & Bone Biology Program, Sydney, NSW, Australia
[c] St. Vincent's Hospital, University of New South Wales, Sydney, Australia
[d] Sydney School of Medicine, University of Notre Dame, Sydney, Australia
[e] Maastricht University Medical Centre/CAPHRI, Department of Internal Medicine, Subdivision of Rheumatology, Maastricht, The Netherlands
[f] University Hasselt, Biomedical Research Institute, Belgium
[g] VieCuri Medical Centre Noord-Limburg, Department of Internal Medicine, Subdivision of Endocrinology, Venlo, The Netherlands
[h] Maastricht University Medical Centre/NUTRIM, Maastricht, The Netherlands
[i] Maastricht University/CAPHRI, Department of Family Medicine, Maastricht, The Netherlands

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ABSTRACT

Objectives: There are two commonly used fracture risk prediction tools FRAX® and Garvan Fracture Risk Calculator (GARVAN-FRC). The objective of this study was to investigate the utility of these tools in daily practice.
Study design: A prospective population-based 5-year follow-up study was conducted in ten general practice centres in the Netherlands. For the analyses, the FRAX® and GARVAN-FRC 10-year absolute risks (FRAX® does not have 5-year risk prediction) for all fractures were used.
Results: Among 506 postmenopausal women aged ≥60 years (mean age: 67.8 ± 5.8 years), 48 (9.5%) sustained a fracture during follow-up. Both tools, using BMD values, distinguish between women who did and did not fracture (10.2% vs. 6.8%, respectively for FRAX® and 32.4% vs. 39.1%, respectively for GARVAN-FRC, $p < 0.0001$) at group level. However, only 8.9% of those who sustained a fracture had an estimated fracture risk ≥20% using FRAX® compared with 53.3% using GARVAN-FRC. Although both underestimated the observed fracture risk, the GARVAN-FRC performed significantly better for women who sustained a fracture (higher sensitivity) and FRAX® for women who did not sustain a fracture (higher specificity). Similar results were obtained using age related cut off points.
Conclusions: The discriminant value of both models is at least as good as models used in other medical conditions; hence they can be used to communicate the fracture risk to patients. However, given differences in the estimated risks between FRAX® and GARVAN-FRC, the significance of the absolute risk must be related to country-specific recommended intervention thresholds to inform the patient.

1. Introduction

FRAX®, developed with support of the World Health Organisation, estimates the 10-year absolute fracture risk for a group of so-called major osteoporotic fractures (clinical spine, hip, forearm and humerus) and for hip fractures separately [1–6]. It is advocated for calculating the individualised fracture risk in persons aged 40 years and over [1].

The Garvan Fracture Risk Calculator (GARVAN-FRC)[2] is also an individualised fracture risk prediction tool, which can be used in persons aged 60 years and over, for calculating the 5- and 10-year risk for hip and all fragility fractures (except fingers and toes). This tool includes fewer risk factors and has been shown to be accurate and reliable [4,7–9]. Both tools can be used with and without including bone mineral density (BMD)[3] [1,4,7–9].

* Corresponding author at: Maastricht University, Department of Family Medicine, PO Box 616, 6200 MD Maastricht, The Netherlands. Tel.: +31 433882272; fax: +31 4336 19344.
E-mail address: tineke.vangeel@maastrichtuniversity.nl (T.A.C.M. van Geel).
[1] Visiting Professor at Maastricht University/CAPHRI, The Netherlands.

[2] GARVAN-FRC, Garvan Fracture Risk Calculator.
[3] BMD, bone mineral density.

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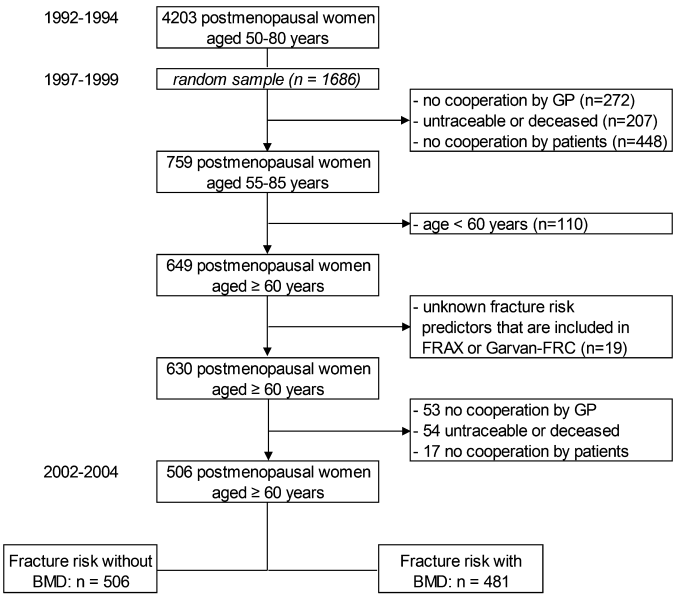

Fig. 1. Flow-chart of patient inclusion: baseline study (1992–1994), 5-year follow-up study, and 10-year follow-up study [11,30].

There are a number of differences between the tools. For example, FRAX® includes more health-related risk factors while the GARVAN-FRC includes number of prior fractures and recent falls [1,4,7–10].

Our objective was to investigate the utility of the FRAX® and GARVAN-FRC fracture risk prediction in a 5-year follow-up study.

2. Materials and methods

2.1. Participants

In 1992–1994 a prospective population-based study was started among twenty general practitioners from 10 general practice centres. In total, 4203 postmenopausal women, who were registered in one of these general practice centres, were willing and able to participate. The methodology of this baseline study has been extensively described elsewhere [11,12]. Five years later, a random sample of 1686 women was invited from the baseline study population and 759 women (45%) were willing and able to participate. Women aged 60–80 years of whom all risk factors needed to complete both risk prediction tools were available, were included ($n = 506$, Fig. 1).

2.2. Measurements

The assessment included bone mineral density measurement (BMD) of the lumbar spine and femoral neck by dual X-ray absorptiometry (Hologic QDR-1000, Hologic Europe, Brussels, Belgium), height and weight measurements. A questionnaire enquired about possible risk factors related to fractures. For FRAX® these include history of prior fracture, parental history of hip fracture, current smoking, use of glucocorticosteroids, presence of rheumatoid arthritis, secondary osteoporosis, and alcohol intake ≥3 units daily. For GARVAN-FRC, these include number of prior fractures and number of prior falls in past 12 months.

Five years later, a questionnaire was completed by all participating women regarding fracture history over the past 5 years. All reported fractures were radiographically confirmed.

2.3. Statistics

SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Descriptive statistics, Chi-square tests, paired and independent *T*-tests were performed to analyse the differences between the 10-year fracture risk with and without BMD based on FRAX® tool for the Netherlands and GARVAN-FRC. In the analysis, the 10-year risk of fracture of individuals was estimated by each tool and then classified into <20% or ≥20% for any osteoporotic fracture, and <3% or ≥3% for hip fractures according to the National Osteoporosis Foundation Guideline advices on drug treatment for FRAX® [6,13], and using age specific cut-off points [14,15].

2.4. Ethics

The study was approved by the medical ethical committee of Maastricht University (MEC 97-068).

3. Results

In total, 506 postmenopausal women aged 60 years and over (mean age: 67.8 ± 5.8 years) were included in this study (Fig. 1). Women who sustained a fracture ($n = 48$, 9.5%) during follow-up were significantly older, had a lower femoral neck BMD (*T*-score), were more likely to have had one or more prior fractures, and more likely to have had one or more falls within the previous year (Table 1). Of the 48 women who sustained a fracture, only 6 (12.5%) sustained a hip fracture, 16 a forearm fracture (33.3%), 6 (12.5%) a shoulder (or humerus) fracture, 5 (10.4%) a clinical spine, and 15 a variety of other low trauma fragility fractures.

Despite major differences in estimated risk, both tools distinguished between women who did and did not fracture at the group level, i.e. the mean estimated fracture risk was significantly higher in women who sustained a fracture than in those who did not (Table 2). Similar results were found when only osteoporotic fractures, based on the FRAX® definition ($n = 33$, 6.9%), were included (Table 2).

The GARVAN-FRC performed significantly better for women who sustained a fracture and FRAX® for women who did not sustain a fracture (Fig. 2A–F).

Using the tools with and without BMD values, of those who sustained a fracture, only 8.9% and 8.3% respectively had an estimated fracture risk ≥20% using FRAX® compared with 53.3% and 52.1% using GARVAN-FRC. These estimates were 42.2% and 68.9%, respectively for an estimated hip fracture risk of ≥3%.

Of those who did not sustain a fracture, 97.2% and 95.2%had an estimated fracture risk <20% using FRAX®, and 68.1% and 67.9% using GARVAN-FRC with and without BMD, respectively. These estimates were 56.7% and 82.8%, respectively for an estimated hip fracture risk of <3%.

The area under the receiver operant curve (AUC), and the sensitivity, specificity, positive and negative predictive values, and the accuracy are stated in Table 3 for various cut-off points. The AUC for a model including age and BMD *T*-score of the femoral neck alone was 0.669, which is lower but not significantly worse than the AUCs (Table 3) based on FRAX® and GARVAN-FRC.

When age-related cut-off points were used [14,15], the results were similar. Of those who sustained a fracture, 6.3% were classified as "consider BMD measurement" using FRAX® (Fig. 3A), while this was 62.5% using GARVAN-FRC (Fig. 3B); and 11.1% were classified as "consider treatment" using FRAX® (Fig. 3C), while this was 66.7% using GARVAN-FRC (Fig. 3D). Of those who did not sustain a fracture, 96.8% and 96.1% were classified as "no treatment required" using FRAX® (Fig. 3A and C), while this was 51.1% and

Table 1
Patient characteristics: comparison between women who sustained ($n = 48$) and did not sustain a fracture ($n = 458$) during follow-up.

	Fracture group ($n = 48$)	Non-fracture group ($n = 458$)	p-Value
Age (years)	69.6 ± 5.9	67.6 ± 5.7	**0.019**
Weight (kg)	71.8 ± 11.2	71.2 ± 12.9	0.751
Height (cm)	158 ± 6.0	160 ± 6.2	0.130
Femoral neck BMD (T-score)	−1.7 ± 1.0	−1.2 ± 1.0	**0.003**
Included only in FRAX®			
History of prior fracture	23 (47.9)	111 (24.2)	**0.001**
Parental hip fracture	4 (8.3)	26 (5.7)	0.514
Current smoking	10 (21.3)	87 (19.0)	0.705
Use of glucocorticoids	3 (6.3)	11 (2.4)	0.139
Rheumatoid arthritis	4 (8.3)	18 (3.9)	0.155
Secondary osteoporosis	9 (18.8)	61 (13.3)	0.300
Alcohol intake ≥3 units daily	1 (2.1)	5 (1.1)	0.453
Included only in GARVAN-FRC			
Number of prior fractures			**0.001**
1	12 (25.0)	62 (13.5)	
2	6 (12.5)	40 (8.7)	
≥3	5 (10.4)	11 (2.4)	
Number of recent prior falls			**0.033**
1	13 (27.1)	88 (19.2)	
2	5 (10.4)	34 (7.4)	
≥3	6 (12.5)	22 (4.8)	

GARVAN-FRC, Garvan Fracture Risk Calculator.

53.5% using GARVAN-FRC (Fig. 3B and D) with and without BMD included, respectively.

Regardless of the chosen cut-off point, GARVAN-FRC has a higher sensitivity, therefore correctly classified more women who sustained a fracture as having a high risk, and FRAX® has a higher specificity, therefore classified more women who did not sustain a fracture as having low risk.

4. Discussion

The 10-year estimated risk was significantly higher in women who, over a 5-year follow-up period, sustained a fracture using FRAX® and GARVAN-FRC compared with women who did not sustain a fracture. The AUCs were similar for both tools. However, the GARVAN-FRC performed significantly better for women who sustained a fracture ($p < 0.0001$) and FRAX® for women who did not sustain a fracture ($p < 0.0001$).

Importantly, although the 10-year fracture risk was approximately 3-fold higher using GARVAN-FRC compared to FRAX®, it still underestimated the observed fracture risk within 5 years. Over a full 10 years of follow-up, additional individuals would be expected to sustain fractures; this would lead to worsening of sensitivity but possible improvement in specificity.

One weakness of this study is that it is based on a 5-year follow-up period rather than the 10-year prediction, and therefore, used the 5-year observed rates. The estimated fracture risks of FRAX® and GARVAN-FRC are non-linear and level off at higher age, since these tools take the 'competing risk' of mortality into account. As the GARVAN-FRC provides 5-year risk as well, this was compared with the actual fracture outcomes over 5 years. Thus, the estimated 5-year risk with BMD in the fracture and non-fracture group were 18.0% and 9.9%, respectively, for all fragility fractures and 8.2% and 3.1%, respectively, for hip fractures. Hence, as might be expected, the sensitivity worsened but specificity was improved. Another limitation is the relatively small sample size (506 women who sustained 48 fractures during follow-up). However, the absolute fracture risk of 9.5% reported in our study is similar to the one reported by Johnell et al. who studied 38,973 men and women from 12 prospective cohorts. The total number of any fracture in these cohorts combined was 3694 (9.5%) [16]. In addition, in our group, only 33 women were treated with bisphosphonates (6.5% of 506) over a mean period of 2.5 years (1.9 SD). Whether this treatment that presumably lowers actual fracture risk leads to falsely raised false positive rate, i.e. worse specificity, is not certain. However, Leslie et al. showed that only in patients who are highly adherent to treatment for a minimum of 5-years was predicted fracture risk significantly higher than observed [17].

Table 2
Estimated fracture risk using FRAX® and Garvan Fracture Risk Calculator (GARVAN-FRC).[a]

	Fracture group		Non-fracture group ($n = 458$)
	All fracture types ($n = 48$)	FRAX® definition[b] ($n = 33$)	
FRAX®			
Osteoporotic fracture risk without BMD (mean ± SD)	11.0 ± 7.2	12.0 ± 7.9	8.1 ± 5.6
Osteoporotic fracture risk with BMD (mean ± SD)[c]	10.2 ± 6.1	11.0 ± 6.5	6.8 ± 5.0
Hip fracture risk with BMD (mean ± SD)[c]	3.2 ± 2.8	3.3 ± 2.7	1.9 ± 3.1
GARVAN-FRC			
Osteoporotic fracture risk without BMD (mean ± SD)	32.9 ± 23.1	35.7 ± 23.9	21.2 ± 15.1
Osteoporotic fracture risk with BMD (mean ± SD)[c]	32.4 ± 22.0	34.7 ± 24.1	19.1 ± 13.8
Hip fracture risk with BMD (mean ± SD)[c]	14.8 ± 16.8	16.9 ± 18.7	5.7 ± 10.2

BMD, bone mineral density.
[a] Estimated fracture risk of FRAX® and GARVAN-FRC were significantly different within each group ($p < 0.001$) and between both fracture groups and non-fracture group ($p < 0.01$).
[b] FRAX® definition of osteoporotic fractures: clinical spine, hip, forearm, shoulder and hip fractures.
[c] Risk with bone mineral density (BMD, bone mineral density): $n = 45$ for fracture all fracture types, $n = 30$ for FRAX® definition, and $n = 436$ for non-fracture group.

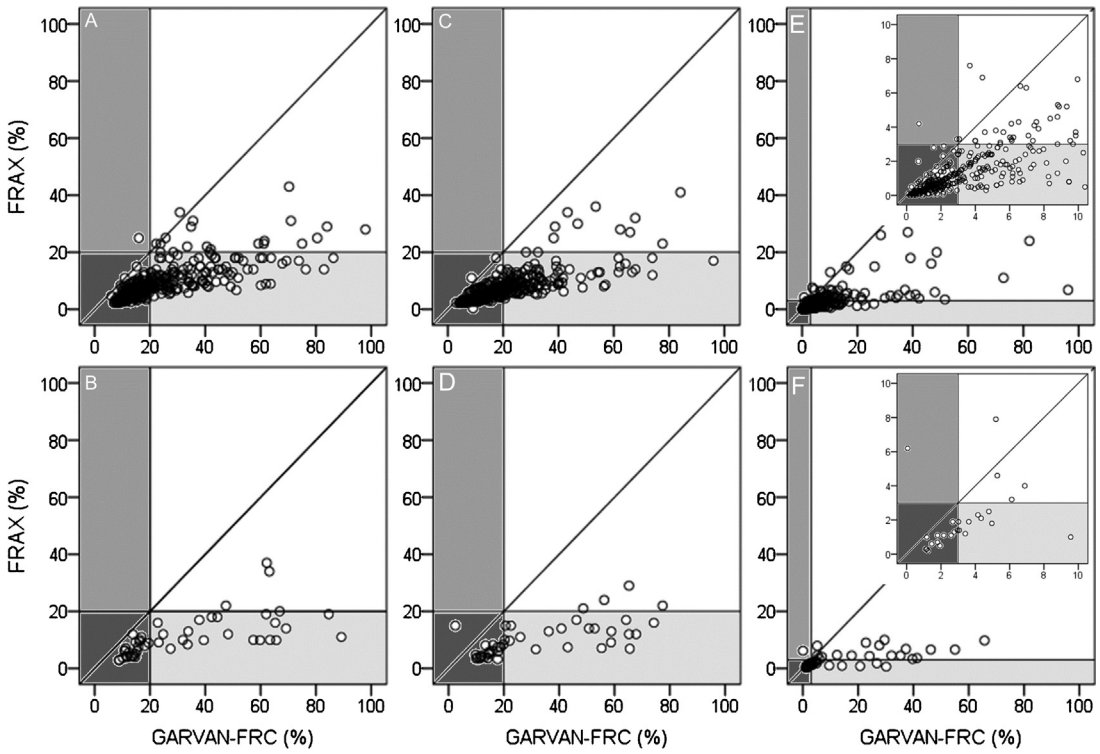

Fig. 2. Estimated 10-year osteoporotic fracture risk without (AB) and with BMD (CD), and hip fracture risk (EF) specified for women who did not (A, C, E) and did sustain a fracture (B, D, F). White area: both tools above cut-off point, light grey area: FRAX® below cut-off point, middle grey area: Garvan fracture risk calculator (GARVAN-FRC) below cut-off point, and dark grey area: both tools below cut-off point.

The AUCs in our study (FRAX® and GARVAN-FRC) were lower than reported in a retrospective cross-sectional Australian study [5] that compared the tools between patients with and without a recent fracture. In women, they reported an AUC of 0.78 for FRAX® UK, 0.84 for FRAX US and 0.84 for GARVAN [5]. In a prospective study [18] including patients with and without calcium supplementation, the AUCs ranged from 0.62 to 0.64 for osteoporotic fractures. In general, validation studies showed a

Table 3
Area under the receiver operant curve (AUC) Sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive value (NPV), and the accuracy (Acc) of FRAX® and Garvan Fracture Risk Calculator (GARVAN-FRC) for several cut-off points.

	AUC	Se	Sp	PPV	NPV	Acc
FRAX®						
Osteoporotic fracture risk without BMD	0.653					
10		45.8	76.9	17.2	93.1	7.4
20 [6,13]		8.3	95.2	15.4	90.8	87.0
30		4.2	99.1	33.3	90.8	90.1
Osteoporotic fracture risk with BMD	0.693					
10		42.2	84.2	21.6	93.4	80.2
20 [6,13]		8.9	97.2	25.0	91.2	89.0
30		0.0	98.9	0.0	90.5	89.6
Hip fracture risk with BMD	0.698					
1.5		60.0	62.4	14.1	93.8	62.2
3.0 [6,13]		42.2	82.8	20.2	93.3	79.0
4.5		31.1	91.2	26.9	92.8	85.7
GARVAN-FRC						
Osteoporotic fracture risk without BMD	0.646					
10		95.8	10.9	10.1	96.2	19.0
20 [6,13]		52.1	67.9	14.5	93.1	66.4
30		43.8	81.9	20.2	93.3	78.3
Osteoporotic fracture risk with BMD	0.689					
10		95.6	23.4	11.4	98.1	30.1
20 [6,13]		53.3	68.1	14.7	93.4	66.7
30		42.2	84.9	22.4	93.4	80.9
Hip fracture risk with BMD	0.695					
1.5		86.7	30.5	11.4	95.7	35.8
3.0 [6,13]		68.9	56.7	14.1	94.6	57.8
4.5		55.6	68.1	15.2	93.7	66.9

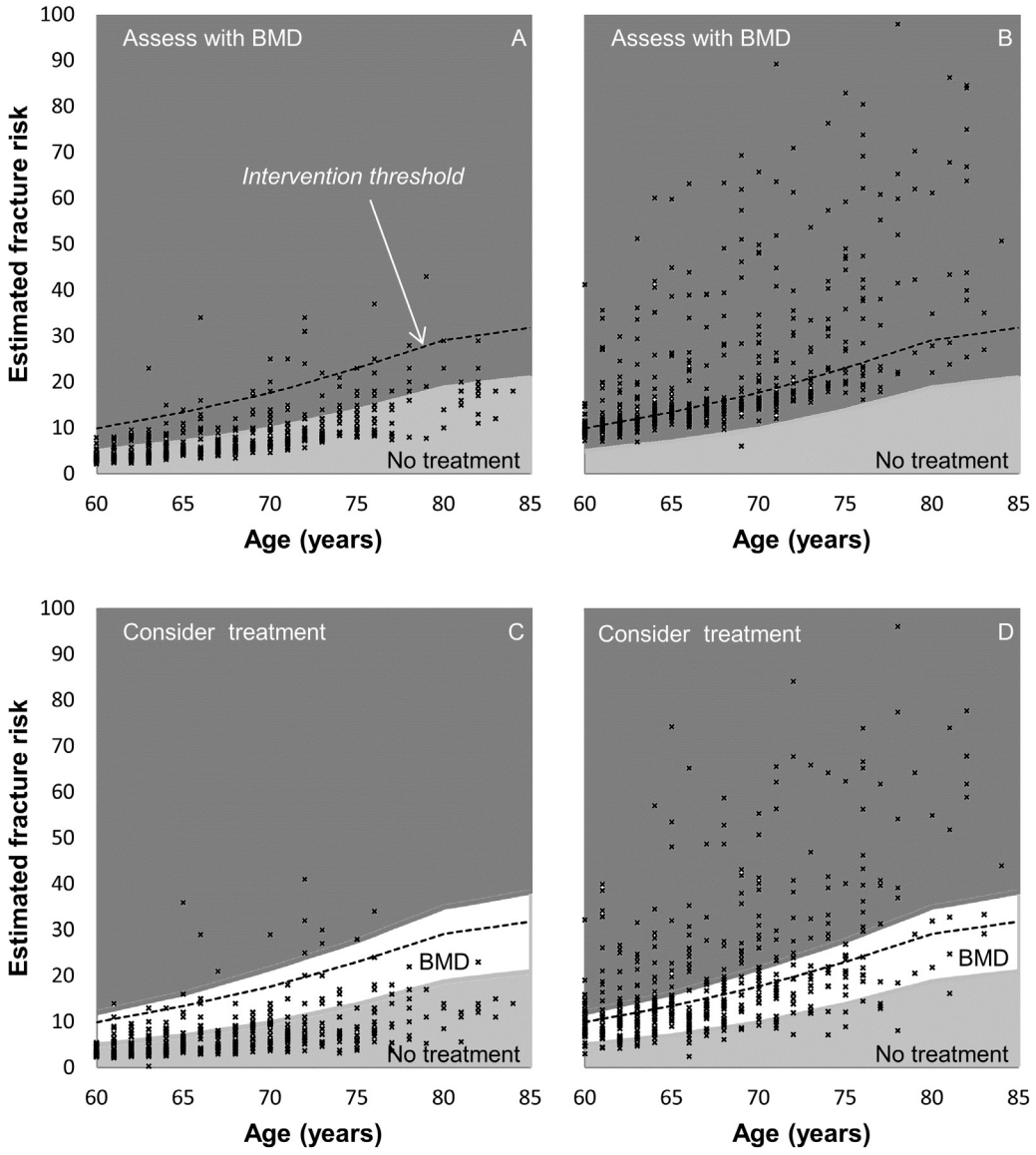

Fig. 3. Estimated 10-year osteoporotic fracture risk without (AB) and with BMD (CD) for FRAX® (A and C) and Garvan fracture risk calculator (GARVAN-FRC; B and D). Assessment and intervention thresholds are age-specific and categorised as: treatment not recommended (light grey area), consider BMD assessment (dark grey area in A and B; white area in C and D), and consider treatment (dark grey area in C and D) [14]. Dotted line (A–D) is the intervention threshold.

AUC range of 0.61–0.83 for FRAX® and 0.63–0.88 for GARVAN-FRC [19–27].

The major differences in predicted risk support the concept that all algorithms require an external validation before clinical implementation [5] and that validation is necessary in local cohorts [18]. In addition, the large overlap in estimated fracture risk between patients with and without fracture indicates that the discriminant ability for individuals is only moderate, which may limit their clinical utility [18]. On the other hand, these AUCs are at least as good as tools used in cardiovascular disease [28,29].

In the study of Bolland et al., the AUCs were similar between these tools and models that included only age and BMD [18]. Thus, including the number of previous fractures and recent falls did increase discrimination compared to age and BMD alone at the group level, and had only moderate discriminant value at the individual level.

In contrast to the moderate discriminant value, GARVAN-FRC has a 3 times higher 10-year absolute fracture risk than FRAX® for women who did fracture and >2.5 times higher for women who did not fracture. Thus, they are quite different with regard to estimated absolute risks, presumably related to the inclusion of different risk factors; for example, the number of previous fractures and recent falls (in the GARVAN-FRC) and the presence of secondary osteoporosis (in FRAX®). In addition, FRAX® calculates the risk for osteoporotic fractures defined as clinical spine, hip, forearm and humerus fracture. Although GARVAN-FRC calculates the risk for all fractures except fingers and toes, including only the FRAX® definition of osteoporotic fractures showed similar results.

The data indicate that, although based on 5-year and not 10-year outcome data, both tools distinguish at the group level between women who did and did not fracture. However, interpretation of the absolute risk per tool is difficult in daily practice. Consider a woman aged 70 years (1.60 m and 60 kg) with a BMD *T*-score of −1.0, a recent prior fracture, two falls in the past year, who smokes and whose mother had fractured a hip. Her 10-year risk is 13% using FRAX® and 45.5% using GARVAN-FRC. Using the FRAX® tool, her estimated fracture risk (13%) is lower than the fracture risk of the general population [30] but is substantially higher (45.5%) using the GARVAN-FRC tool. Due to the major difference in risk estimates, it is unclear what message a clinician would deliver. Hence these

risk estimates have to be provided alongside national and ethnic specific recommendations about treatment thresholds.

5. Conclusion

The implications of these risk estimate differences deserve careful consideration. Some of those predicted to be at moderately high risk but who had not yet sustained a fracture within 5 years could be expected to sustain a fracture over the next 5 years. As individuals without fractures in the first 5 years would move to the fracture group over the next 5 years, the sensitivity of both tools would decrease while their specificity would increase. Despite these limitations, the fracture risk assessment tools are at least as good as tools used for cardiovascular disease [28,29], and can still be used to help clinicians to communicate the fracture risk to their patients [19]. Due to the differences in predicted risk, the significance of the absolute risk should be communicated to each person in relation to country-specific intervention threshold recommendations.

Contributors

All authors were responsible for the design of the study. TACMG undertook the analysis and all authors were responsible for the interpretation of the data. TACMG drafted the manuscript and all authors were responsible for revised versions of the manuscript. All authors have approved the final version.

Competing interests

JAE and JRC developed the Garvan Fracture Risk Calculator. All other authors state that they have no conflicts of interest with regard to this study.

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Ethics

The study was approved by the medical ethical committee of Maastricht University (MEC 97-068).

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