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REVIEW

SIGN Guidelines for Scotland: BMD Versus FRAX Versus QFracture

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Abstract Scottish Intercollegiate Guidelines Network (SIGN) recently issued guidance on the management of osteoporosis and the prevention of fragility fractures. The aim of this paper was to critically review the guidance. The SIGN guidance utilises risk factors for fracture as an initial step for assessment, but recommends treatment only in individuals with a T-score of −2.5. There are many problems with the sole use of BMD as the sole gateway to treatment. Moreover, the assessment tools to determine risk (FRAX or QFracture) are not designed to detect osteoporosis but rather fracture risk. Whereas SIGN assumes that FRAX overestimates fracture probability, there are compelling reasons to believe that the disparity is related to the inadequate calibration of QFracture. The disparities make the use of a single threshold for BMD testing problematic. The SIGN guidance for men at high risk of fracture provides a set of confused and inconsistent recommendations that are in direct conflict with regulatory authorizations and is likely to increase further the large treatment gap in men. For women, the number of women eligible for treatment (i.e. with osteoporosis) is 81,700 with the use of FRAX but only 12,300 with QFracture representing 8.2 and 1.2 % of the total population at risk, respectively. We conclude that serious problems with the SIGN guidance preclude its implementation.

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Introduction

The advent of fracture risk assessment tools has resulted in the incorporation of FRAX and other tools into many guidelines for the management of osteoporosis [1].

In March this year, the Scottish Intercollegiate Guidelines Network (SIGN) issued guidance on the management of osteoporosis and the prevention of fragility fractures [2]. These represent a departure from earlier guidelines in the use of risk assessment algorithms recently approved by National Institute for Health and Care Excellence (NICE) in the UK [3].

The assessment algorithm is summarised in Fig. 1. In brief, there are different pathways for patients with a prior fragility fracture and those with other clinical risk factors for fracture. Patients with a prior fragility fracture are assessed by DXA (at the spine or hip) and treatment considered in patients with a T-score diagnosis of osteoporosis. There is an exception for a prior vertebral fracture (not defined) or prior hip fracture where BMD testing is left to the physician's discretion. In the case of men and women aged 50 years or more without a prior fracture, individuals are screened using other clinical risk factors (Table 1). In the presence of clinical risk factors, fracture risk is assessed either with QFracture® or FRAX® (but preferentially the former). Where the cumulative 10-year incidence of major osteoporotic fracture (10-year probability in the case of FRAX) equals or exceeds 10 %, then a BMD test is recommended and treatment considered in patients with a T-score diagnosis of osteoporosis.

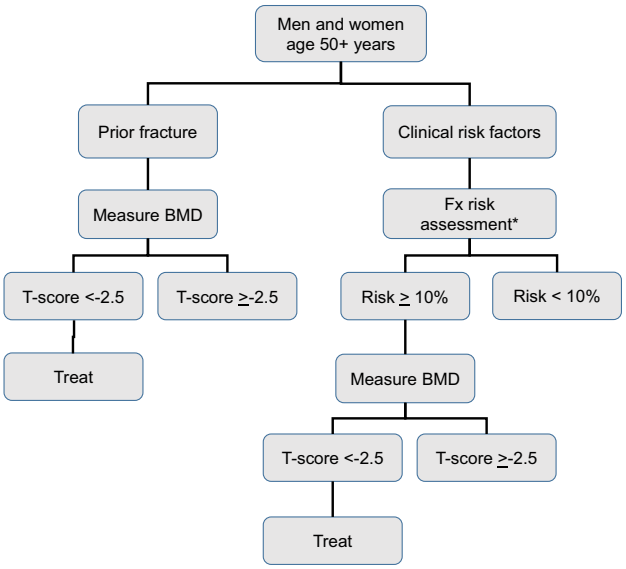

Fig. 1 Summary of assessment algorithm in the SIGN guidance

This paper reviews some of the problems with the application of these guidelines. The major issues arise in the use of BMD as the principal gateway to treatment, the reliance on QFracture, the setting of intervention thresholds and the budget impact of the guidelines.

Choice of BMD Thresholds

In many countries, intervention thresholds have historically been based on the T-score for BMD but in recent years have been replaced by the use of more complete risk assessment tools [1, 4–6]. Against this shift, the SIGN guidance firmly entrenches a T-score threshold of −2.5 SD, reminiscent of European and UK guidance nearly 20 years ago [7, 8]. Since then several factors have been identified that make the use of this T-score problematic as an intervention threshold [9].

Table 1 Risk factors associated with fragility fracture which should prompt consideration of fracture risk assessment [2]

Risk factor	Criteria	Caveat	Action
Previous fragility fracture	–	>50 years	DXA
Parental history of osteoporosis	–		FRA
History of early menopause (below age of 45)	Untreated	>50 years	FRA*
Low BMI	<20 kg/m^2	>50 years	FRA
Smoking	Current	>50 years	FRA*
Low bone mineral density	Not defined	none	FRA
Alcohol intake	>3.5 units per day	>50 years	FRA
Diabetes	–	>50 years	FRA*
Inflammatory rheumatic diseases (RA or SLE)	–	>50 years	FRA*
Inflammatory bowel disease and malabsorption	–	>50 years	FRA*
Institutionalised patients with epilepsy	–	>50 years	FRA*
Primary hyperparathyroidism and endocrine diseases	–	>50 years	FRA*
Chronic liver disease	–	>50 years	FRA*
Neurological diseases (including Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke)	–	>50 years	FRA*
Chronic kidney disease	GFR 30–60 ml/min/1.73 m^2	>50 years	FRA*
Asthma	–	>50 years	FRA*
Long-term antidepressants	SSRI	>50 years	FRA*
Antiepileptics		>50 years	FRA*
Aromatase inhibitors	Women	>50 years	FRA*
GnRH agonists (in men with prostate cancer)	Men	>50 years	FRA*
Proton pump inhibitors	–	>50 years	FRA*
Oral glucocorticoids	–		FRA
Thiazolidinediones for diabetes		>50 years	FRA*

FRA fracture risk assessment; *FRA** fracture risk assessment particularly in the presence of other risk factors; *DXA* dual-energy X-ray absorptiometry; *RA* rheumatoid arthritis; *SLE* systemic lupus erythematosus; *GnRH* agonists, gonadotropin-releasing hormone; *SSRI* selective serotonin reuptake inhibitors

First, although reduced bone mass is an important and easily quantifiable measurement, most fragility fractures occur in individuals with a BMD T-score above the operational threshold for osteoporosis [10, 11]. The problem arises because BMD captures the likelihood of fracture incompletely. There is an appropriate analogy with several other multi-factorial diseases, such as hypertension and stroke. Blood pressure is continuously distributed in the population (as is BMD) and hypertension is an important cause of stroke (high specificity). But a majority of individuals with stroke are normotensive (low sensitivity) [12].

A second factor relates to the fact that any given T-score threshold has a different significance at different ages [13]. At the age of 65 years, a T-score of −2.5 SD confers a significant increase in the probability of fracture compared with women with no clinical risk factors and in whom BMD is not measured. With advancing age, the difference in the probability of fracture between the general population and those with a T-score of −2.5 SD diminishes and indeed, from the age of 80 years onwards in the UK, the fracture probability becomes progressively lower than that of the age and sex-matched general population with no clinical risk factors (Fig. 2). In other words, a T-score of −2.5 SD becomes a protective factor from the age of 80 years. The reasons relate to the decreasing BMD in the general population with age and the higher competing effect of mortality with age.

Whereas a prior fracture confers an increase in risk at all ages, the addition of BMD to the risk assessment attenuates the impact of a prior fracture on fracture probability at older ages (see Fig. 2).

The SIGN guidance defends its position by stating "that the beneficial effects [of treatment] on fracture risk is restricted to patients with osteoporosis as defined by the presence of pre-existing vertebral fractures and or those with BMD values that lie within or close to the osteoporotic range". The argument presupposes that high FRAX scores with or without BMD does not identify individuals with low bone mineral density—a supposition that is ill-founded [14–16]. An example of the application of the guidelines used by the National Osteoporosis Guideline Group (NOGG) in the UK is given in Table 2, which shows that the case-finding strategy identifies women with low BMD. Moreover, the conclusion that these drugs only act in BMD proven osteoporosis is a flawed one, driven by subgroup analyses, most of which are post hoc [17]. Indeed, the relevant question in a more statistically appropriate manner is; is there an interaction between the effect of treatment and baseline BMD? All studies that have examined this for the outcome of vertebral fractures have not shown any impact of baseline BMD on risk reduction during therapy.

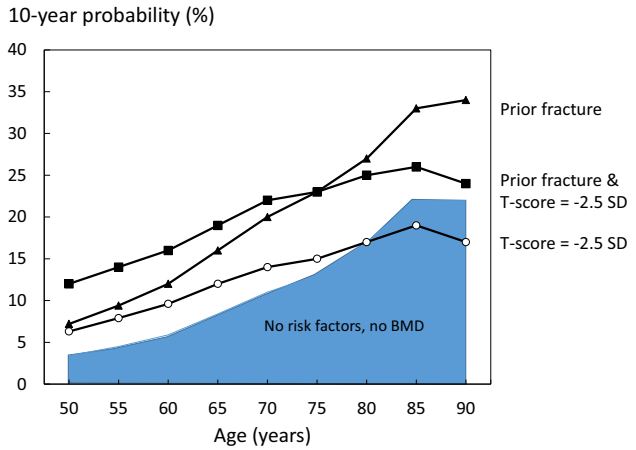

Fig. 2 10-year probabilities (%) of a major osteoporotic fracture for women from the UK according to a T-score of −2.5 SD (*open circle*), prior fracture (*solid triangle*) or the combination (*solid square*) (BMI is set to 24 kg/m^2). [http://www.shef.ac.uk/FRAX]. Note the stable probability after the age of 85 years due to the competing effect of mortality

Fracture Risk Assessment

The SIGN guidance focuses on two risk assessment tools, QFracture and FRAX, the comparative features of which are summarised in Table 3.

QFracture 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 years (http://www.qfracture.org). It has been internally validated (i.e. from a stratum of the same population) and also externally validated in the UK in other general practitioner databases [18, 19]. It takes into account numerous risk factors elicited from general practitioner records (Table 4). The output is the 1–10 year cumulative incidence of a major osteoporotic fracture (hip, spine, shoulder or wrist fracture) or hip fracture alone.

FRAX (http://www.shef.ac.uk/FRAX) provides models for the assessment of fracture probability in men and women [20, 21]. The tool is widely validated and calibrated to the country in which it is used. The approach uses easily obtained clinical risk factors to estimate 10-year fracture probability. The estimate can be used alone or with BMD to enhance fracture risk prediction [14, 22]. In addition to fracture risk, FRAX uses Poisson regression to derive hazard functions of death. These hazard functions are continuous as a function of time, which permits the calculation of the 10-year probability of a major fracture and the 10-year probability of hip fracture.

Like the FRAX tool, QFracture takes into account history of smoking, alcohol, glucocorticoid use, parental history (of hip fracture or osteoporosis) and several secondary causes of osteoporosis. There are, however, differences in

Table 2 NOGG strategy applied to women from without prior fracture, by age (/1000) [14] with kind permission from Springer Science + Business Media B.V

Age (years)	Number scanned	Number selected	Expected hip fractures	Expected MOF	Mean FN T-score
50	63	22	2	52	−1.78
55	48	16	2	27	−2.28
60	59	14	2	17	−2.67
65	131	38	7	48	−2.58
70	140	29	8	38	−2.91
75	89	18	6	23	−3.35
80	69	15	6	16	−3.60
85	50	15	7	20	−3.66
			40	241	

FN femoral neck; *MOF* major osteoporotic fracture (hip, clinical spine, forearm, proximal humerus)

Table 3 Comparative features of QFracture and FRAX

	QFracture	FRAX
Externally validated	Yes (UK only)	Yes, internationally
Calibrated	Yes (hip only)	Yes
Applicability	UK	57 countries
Falls as an input variable	Yes	No
BMD as an input variable	No	Yes
Prior fracture as an input variable	Yes	Yes
Family history as an input variable	Yes	Yes
Outcome	Hip, forearm, spine, shoulder	Hip, forearm, spine, humerus
Outcome metric	Incidence	Probability

the construct of questions (Table 4). Unlike FRAX, QFracture cannot be used with BMD. The most important difference is in the output. QFracture provides the 1–10 year cumulative incidence in survivors of a major osteoporotic or hip fracture. In contrast, the output of FRAX is 10-year probability, which takes account of the competing risk of death. Apart from age, some of the risk factors incorporated affect the risk of death as well as the risk of fracture. Examples include low BMD and smoking. In the case of age and BMD, the effect is modest since the two hazard functions have an opposing influence on fracture probability.

The SIGN guidance reviews the available risk assessment tools. Whereas it acknowledges the position of NICE that both FRAX and QFracture can be used [3], QFracture is the preferred tool. To use its words, the argument runs that "The main strength of QFracture over other calculators is that it has been extensively validated in the UK population and has been shown to be more accurate at predicting fractures in the UK population than FRAX".

The guidance further states that "the FRAX algorithm underestimates the 10-year fracture risk in older people compared with Qfracture. This has been attributed to the fact that FRAX takes the mortality rate of the general population into account when making the fracture calculation whereas the other calculators do not [23, 24]. Whilst the QFracture algorithm does not take mortality into account it has been shown to accurately predict fracture risk in older people up to the age of 85 years. This suggests that FRAX underestimates fracture risk, rather than QFracture overestimating fracture risk".

These textual extracts are extraordinary. At best, they display a fault of logic. The logical error is to use a fracture risk assessment tool to determine who has osteoporosis. QFracture is not designed to identify low BMD and is expected to have low sensitivity for the detection of osteoporosis. FRAX can be used without BMD but its optimal use is to determine who should have a BMD test to improve fracture prediction with the FRAX algorithm.

Neither QFracture nor FRAX are designed to identify low BMD. If the detection of osteoporosis is the goal, then why choose a tool designed for the prediction of fracture when there are many more appropriate tools available for the detection of osteoporosis [20, 25]? In one study, for example, the sensitivity of FRAX (i.e. the detection rate for osteoporosis) at a similar fracture threshold (9.3 %) was 33.3 %, whereas the Osteoporosis Self-Assessment Tool (OST) [26] had, in the same population, a sensitivity of 79.3 % [27, 28]. Sensitivities in the order of 90 % or more are reported in other populations [28]. Moreover, these

Table 4 Risk factors for fracture used in QFracture and FRAX

	QFracture	FRAX
In common		
Age		
Sex		
Body mass index	Optional	
Prior fracture[a]		
Smoking[a]	6 categories	
Parental history[a]		
Alcohol[a]	6 categories	
Rheumatoid arthritis		
Glucocorticoids[a]		
Diabetes type 1		
Chronic liver disease		
Malabsorption		
Hyperparathyroidism		
FRAX only		
Bone mineral density		Optional
Osteogenesis imperfecta in adults		
Hypogonadism		
Premature menopause		
Malnutrition		
QFracture only		
Diabetes type 2		
Nursing home		
Ethnicity		
Fall history		
Dementia		
Cancer		
Asthma or COPD		
Heart attack, angina, stroke or TIA		
Chronic kidney disease		
Parkinson's disease		
SLE		
Thyrotoxicosis, Cushing's syndrome		
Epilepsy or taking anticonvulsants		
Taking antidepressants		
Taking oestrogen only HRT		

Risk factors, other than BMD and BMI, are dichotomised (yes/no) unless otherwise indicated

[a] Question construct differs

instruments are easier to administer than FRAX or QFracture; OST is calculated only from weight and age. If the intention of screening had been to identify women at a high risk, then a fracture risk assessment algorithm would be the appropriate tool. In this context, FRAX outperforms OST for fracture prediction [22].

The error of logic is compounded by, at best, an uncritical review of the respective performance characteristics of QFracture and FRAX that leads SIGN to favour QFracture over FRAX. The argument takes an extremely blinkered view of the evidence available. It is true that QFracture and FRAX are comparably calibrated for hip fracture risk [5, 29]. This is confirmed in Fig. 3 where the 10-year hip fracture rates/probabilities are shown in women at each decile of risk category [30]. In contrast, a quite different pattern is evident for a major osteoporotic fracture (the outcome used by SIGN) where the rates/probabilities are markedly higher in the case of FRAX for any category of risk [31, 32].

Whereas SIGN naively assumes that FRAX overestimates fracture probability (but states that FRAX underestimates fracture risk a few lines later in the text), there are compelling reasons to believe that the disparity is related to the inadequate calibration of QFracture.

(1) GP records are reasonably accurate for the documentation of hip fracture but notoriously unreliable for other major fractures, particularly vertebral fractures [33]. The prevalence of a prior major fracture in the QFracture database is 1.9 % [29], whereas prior fracture is estimated at 21–45 % in women from the UK, depending on age. Of these, approximately half will be major fractures [14]. For a parental history of osteoporosis or hip fracture, the prevalence is given at 0.3 % in the QFracture database, whereas meta-analysis of prospective studies give a prevalence of parental hip fracture at 13 % [34]. The impact of the inaccuracies is difficult to quantify but is likely to decrease the median of the distribution of 10-year risk in the population. Empirical observation supports this view in that at each tenth of risk category, QFracture risk is lower than FRAX-based probabilities (see Fig. 3).

(2) The poor and inaccurate capture of clinical risk factors is likely to bias their weights for both hip fracture risk and major fracture risk. This is evident

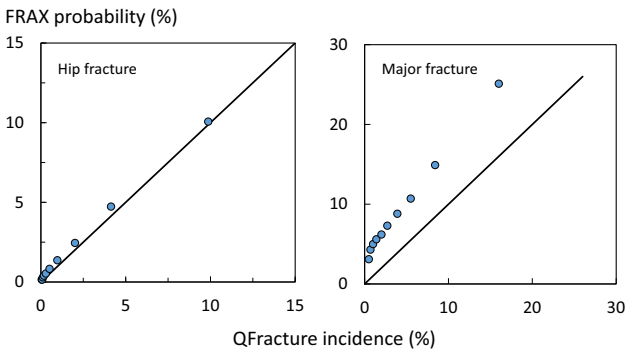

Fig. 3 Comparison of the distribution of FRAX and QFracture (QF) model output by decile of risk in women for hip fracture (*left panel* [28] and major fracture (*right panel*). The *diagonal line* shows the line of identity [31]

from the example given in Fig. 4 that illustrates the impact of a past fracture on probability and incidence. In the case of FRAX, the probability of fracture is approximately doubled with a prior history of fracture consistent with worldwide observation [35, 36]. As expected from the meta-analysis, the impact of a prior fracture is somewhat greater at younger ages [36]. In contrast, the weighting given for a prior fracture as a risk fracture is unrealistic for QFracture. Thus, in the case of major fracture incidence, QFracture determines an increase in risk ratio of approximately only 8 %, rather than the expected doubling of risk.

(3) As expected, FRAX probabilities of a major fracture exceed that of hip fracture at all ages. In the case of QFracture, the incidence of hip fracture and the incidence of major fracture (in the example in Fig. 4) are identical from the age of 85 years. This implies that no fractures of the spine, humerus or distal forearm arise in women from the age of 85 years. Again, this contrasts with empirical observation [37–39]. Indeed, fragility fractures other than hip fracture account for 64–67 % of fractures in women and men (respectively) aged 85–89 years [37]. There are many other such examples.

(4) It is reported that the QFracture algorithm is not internally consistent when applied at different ages. For example, the 1-year risk of fracture in a 55-year old is lower than the 1-year risk of fracture predicted for the 5th year in a patient aged 50 years [31].

These considerations indicate that little credence can be afforded for estimates of major fracture using the QFracture algorithm. They further indicate that the weights given to several of the clinical risk factors are inappropriate. Both factors result in a large underestimation of major fracture risk by QFracture. In contrast, the prediction of major fractures has been extensively validated with the use of FRAX [22, 38, 39, 41]. In summary, FRAX is well calibrated, whereas QFracture under-predicts risk at all levels of risk.

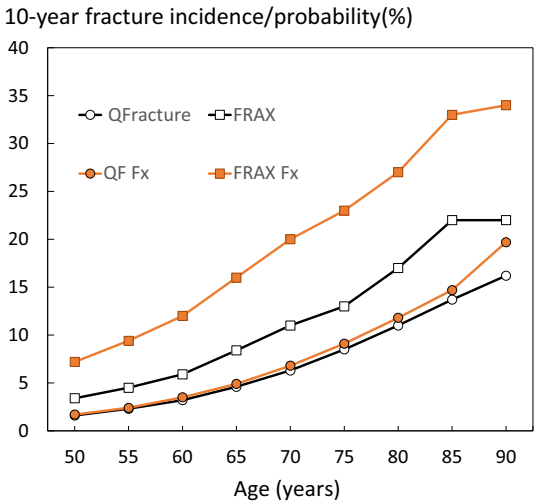

Fig. 4 Comparison of the risk of a major fracture using FRAX and QFracture in women with a BMI of 25 kg/m^2 by age and no clinical risk factors (*open symbols*) and in women with a prior fragility fracture prior fracture (Fx, *solid symbols*)

Assessment Threshold

The SIGN guideline group suggest a fracture risk threshold of 10 % to indicate the need for further assessment with DXA. It does not, however, use the information provided thereby in a treatment decision. Patients are 'punished' twice in that to merit treatment, they must have a fracture risk of 10 % or more AND a T-score of −2.5 SD or less. Bizarre but not improbable scenarios arise. For example, consider a 65-year old woman (BMI set at 25 kg/m^2) whose mother had sustained a hip fracture. Her 10-year fracture probability (16 %) earns her a BMD test. The decision to treat rests solely on her T-score. At a T-score of −2.5 SD, the threshold of osteoporosis, she can be offered treatment but is denied treatment with a T-score of −2.0 SD, even though her risk is higher than the FRAX assessment without BMD (increased from 16 to 18 %).

The SIGN guidance does not distinguish the output from FRAX and QFracture. In other words, the 10 % threshold is used irrespective of the assessment tool that is used. Since the units of measurement differ (cumulative incidence for QFracture and probability for FRAX) together with the problems of calibration, clinical decisions will also differ. Indeed, in the example above, the patient would not qualify even for a BMD test given that her QFracture incidence is 7.2 %.

It is evident that a 10 % threshold for QFracture is at best clinically confusing. Ironically, this fulfils the first statement of intent of SIGN that "this guideline is not intended to be construed or to serve as a standard of care".

Scope of Guidelines

Surprisingly, and contrary to recommended practice, there is no clear description of the population targeted by the guideline. Although men are included in the discussion on some but not all aspects of fracture risk assessment, they are not included in the algorithm that describes the recommended pathway from risk assessment to pharmacological therapy. It is not stated whether the 10 % fracture risk intervention threshold applies to men as well as to women and nowhere in the guideline is it specified whether

Table 5 Number of women in Scotland having FRAX probability (major osteoporotic fracture) and QFracture incidence for major osteoporotic fracture (osteoporotic fracture) above the limit of 10 % and having osteoporosis (BMD FN ≤ -2.5 SD)

Age interval (years)	Estimated population	Number of women above a 10 % threshold		Number of women above 10 % threshold with no previous fracture		Number of women above 10 % threshold having osteoporosis without previous fracture	
		FRAX > 10 %	QFracture > 10 %	With FRAX	With QFracture	Due to FRAX	Due to QFracture
50–59	343,800	47,800	300	6,900	0	800	0
60–69	290,600	141,500	9600	60,700	600	10,000	100
70–79	207,000	191,500	31,500	119,200	5600	31,400	2000
80–89	119,800	119,500	54,600	71,500	15,300	29,400	7100
90–99	31,300	31,200	18,000	17,300	5000	10,100	3100
	992,500	531,500	114,000	275,600	26,500	81,700	12,300

osteoporosis in men should be defined according to male or female reference data. Thus, the indications for treating men with osteoporosis are unclear.

Moreover, the recommendations on pharmacological interventions in men with osteoporosis are confusing and inconsistent. For example, it appears that men with a previous vertebral fracture may be considered for treatment but not those with a history of hip fracture. The confusion over treatment in men continues with the selection of pharmacological agent. Regulatory authorities approve the use of pharmacological interventions in men on the basis of BMD bridging studies for drugs that have been shown to reduce fractures in postmenopausal women. The SIGN guidance then states that it is not possible to recommend alendronic acid in men because there are inadequate fracture data, even though changes in BMD are similar to those in postmenopausal women. Indeed, the guidance recommends against treatment with any of the available (and approved) drugs in men at high risk of osteoporosis (except those taking glucocorticoids).

Overall, the SIGN guidance for men at high risk of fracture provides a set of confused and inconsistent recommendations that are in direct conflict with regulatory authorisations and will increase further the already large treatment gap in men.

Impact of Guidelines

The SIGN guidance makes no statement regarding the impact of its recommendations on clinical practice. The available evidence would suggest that 11.1 % of women and 0.4 % of men aged between 40 and 85 years would be identified for a BMD test using QFracture [30]. The age range is, however, not appropriate for the SIGN guidance (50 + years) and the population demography of Scotland differs from that of the rest of the UK [42]. Unfortunately, a request to Professor Hippisley-Cox to supply age and sex-specific distributions of QFracture remained unanswered but an approximation can be made of the impact of the SIGN guidelines in Scotland.

The estimated female population of Scotland is shown in Table 5 by age. From the distributions of QFracture incidence and FRAX probabilities in THIN [30], the number of women in Scotland with a fracture risk of 10 % or more can be estimated. From a total population of nearly 1 million women aged 50 years or more 531,500 (54 %) would be identified as having a 10-year FRAX probability of 10 % or more. In contrast, nearly 5 times fewer women would be identified above the 10 % threshold with the use of QFracture (114,000, 11.5 %). These figures overestimate the use of FRAX and QFracture since these tests are not to be administered to women with a prior fragility fracture who, under the guidance, should be referred for BMD testing. From the distribution of prior fracture in the UK [14], the number of women eligible for testing falls to 275,600 in the case of FRAX and 26,500 for QFracture (28 and 3 % of the total population, respectively). The number of women eligible for treatment (i.e. with osteoporosis) is 81,700 with the use of FRAX and 12,300 with QFracture representing 8.2 and 1.2 % of the total population, respectively.

In those selected for treatment, the average 10-year risk with QFracture is 13 % and the average 10-year probability with FRAX is 19 %. It is evident that the two assessment algorithms identify widely different populations, which in turn has a marked effect on who receives treatment. For example, no women up to the age of 60 years would be eligible for treatment using QFracture, whereas 12 % of women would be eligible for treatment with FRAX. Clearly, the assumption that the two assessment tools can be used interchangeably is unsafe.

Patients with a prior fragility fracture are advised to have a BMD test and treatment is recommended in those in whom the T-score is less than -2.5 SD. There is an

Table 6 Number of women in Scotland with prior fragility fracture and eligibility for treatment

Age interval (years)	Estimated population	Previous fracture	Osteoporosis and previous fracture	Fracture patients eligible (%)
50–59	343,800	81,100	8300	10.2
60–69	290,600	83,400	16,300	19.5
70–79	207,000	72,500	23,600	32.6
80–89	119,800	48,000	24,300	50.6
90–99	31,300	14,000	10,000	71.4
	992,500	299,000	82,500	27.6

exception for a prior vertebral fracture (not defined) or prior hip fracture where BMD testing is left to the physician's discretion. Overall, only 28 % of women with a prior fragility fracture would be eligible for treatment, ranging from 10 % below the age of 60 years to 71 % between the ages of 90–99 years (Table 6).

Conclusions

We conclude that *s*erious problems with the SIGN guidance preclude its implementation. In addition, the use of QFracture should be reserved only for the assessment of hip fracture risk and little credence can be afforded for estimates of major fracture when using the QFracture algorithm.

Compliance with Ethical Standards

Conflict 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. Professor Compston is Chairman of the National Osteoporosis Guideline Group, UK of which Professors Cooper, Kanis and McCloskey are members of its advisory body.

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