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Position Paper

A New Approach to the Development of Assessment Guidelines for Osteoporosis

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Introduction

An increasing awareness of osteoporosis, combined with the development of treatments with proven efficacy, will increase demand for the more effective management of patients with osteoporosis. This in turn will require widespread facilities for the diagnosis and management of osteoporosis. Measurements of bone mineral are a central component of any provision that arises from the internationally agreed definition of osteoporosis, i.e., a systematic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1,2]. The diagnosis of osteoporosis thus centers on the assessment of bone mass and quality. Since there are no satisfactory clinical tools widely available to assess bone quality, the diagnosis of osteoporosis depends at present upon the measurement of skeletal mass [3].

The clinical significance of osteoporosis lies in the fractures that arise, with their attendant morbidity and mortality. Low bone mass is an important component of the risk of fracture, but other skeletal abnormalities contribute to bone fragility. In addition, a variety of nonskeletal factors contribute to fracture risk, particularly those related to falls. Thus, ideally the assessment of fracture risk should encompass all these aspects of risk. For this reason, there is a distinction to be made between the diagnosis of osteoporosis and the assessment of risk. This in turn implies a distinction between diagnostic and intervention thresholds. Although diagnostic thresholds have been defined [3], this paper summarizes the approach by which intervention thresholds might be defined for clinical practice.

Background

In recent years, a number of approaches to the assessment of osteoporosis have been formulated based on a case-finding strategy. In Europe, the approach recommended by the European Foundation for Osteoporosis (now the International Osteoporosis Foundation,

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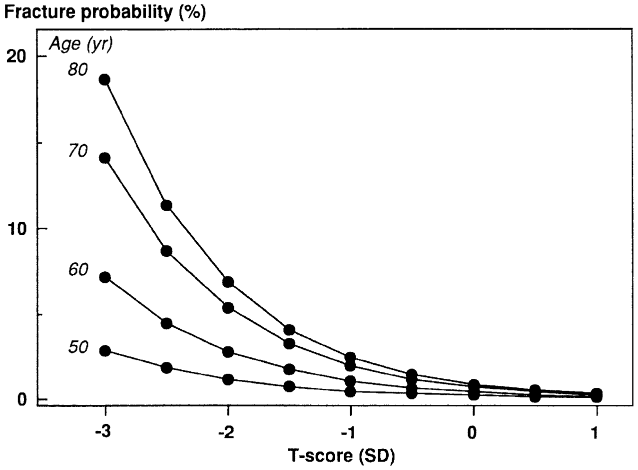

Fig. 1. Ten-year probability (%) of hip fracture in Swedish women according to age and *T*-score for bone mineral density at the femoral neck [9].

IOF) was to identify individuals on the basis of strong risk factors such as prior fragility fractures, corticosteroid use, family history and low body mass index [4–7]. Individuals with such risk factors are assessed thereafter by measurement of bone mineral density (BMD) and treatment is offered in the presence of osteoporosis as defined by the WHO criteria [3]. There are advantages and disadvantages with this approach. An advantage is that guidelines are intuitive to the practice of medicine in that the sequence of clinical practice is to alert suspicion, make a diagnosis and thereafter to treat. A further advantage is that they are conservative in that all individuals identified have a high risk of fracture. Therein also lies a disadvantage in so far as many individuals at high risk go undetected. A further drawback is that the iintervention threshold is set at the diagnostic threshold – a *T*-score of −2.5 SD or less.

It is now evident that the *T*-score has a different prognostic significance at different ages [8,9] (Fig. 1). Moreover, there are many risk factors in addition to age that provide information on fracture risk over and above that provided by BMD alone. Thus, diagnostic thresholds are not equivalent to intervention thresholds since the range of risk varies so markedly at any given BMD.

In 1995, a development committee of the National Osteoporosis Foundation (NOF) began a detailed assessment of the elements required to develop guidelines [10,11]. An important concept developed was the view that intervention thresholds should be modulated according to risk. For example, a prior fragility fracture increases the risk of a further fracture even after adjustment for BMD. The argument runs that, if it is cost-effective to treat all individuals with a *T*-score of −2.5 SD, then it is worthwhile to treat patients with a prior history of fracture at a *T*-score that is somewhat less stringent than −2.5 SD. The NOF provided detailed assessment and intervention strategies based on the modulation of the *T*-score (or *Z*-score) in the presence of various risk factors. The intervention thresholds were defined, however, by cost-effectiveness analysis of questionable relevance to other countries [12]. Moreover, as with the approach of the IOF it has also become evident that the use of *T*-scores or *Z*-scores is problematic in general practice. They are not readily understood or used by primary care physicians. In addition, there has been an enormous increase in the number of validated assessment techniques, each with different performance characteristics. Thus, the *T*-score derived from one site has a different prognostic meaning from the same *T*-score at another site, or at the same site but with a different methodology [13,14]. The use of relative risks is also problematic. For example, the relative risk of fracture for a given BMD decreases with age [15], whereas the incidence of fracture rises (Fig. 2). This is confusing for clinicians.

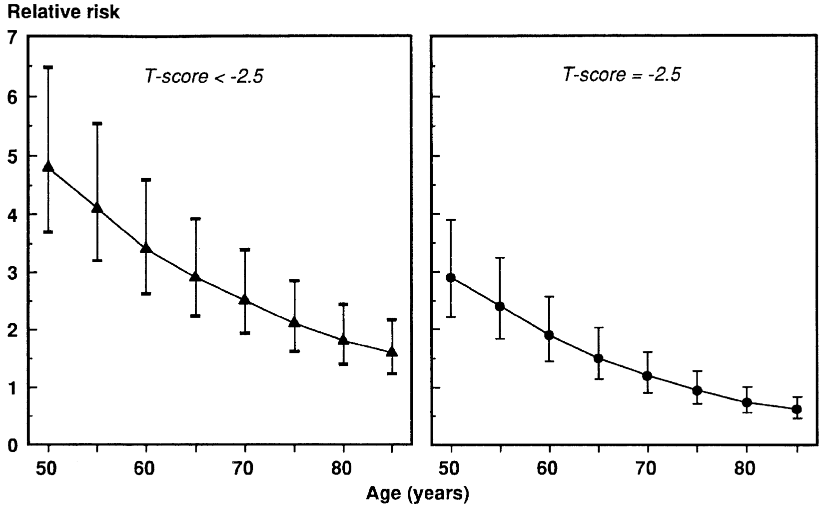

Fig. 2. Population relative risks for hip fracture over 10 years in Swedish women with osteoporosis according to age. Risk is shown for women at the threshold value for osteoporosis ($T = -2.5$ SD) or those below the threshold ($T < -2.5$ SD). Hip fracture risk is assumed to increase 2.6-fold per 1 SD change in BMD ± the 95% confidence estimate of the gradient [15].

These considerations have led to the view that intervention thresholds should be based on absolute risk, i.e., probability of fracture [14,16]. This probability should be derived not only from age and sex, but also from validated risk assessment tools, including but not limited to bone mass measurements. The use of absolute fracture risk has the potential to be applicable to both sexes, all ages, all races and all countries even though the incidence of osteoporotic fractures varies widely by age, gender, ethnicity and geography. Similar approaches are now used in the management of cardiovascular diseases [17–21]. In cardiovascular disease, the simultaneous consideration of smoking, blood pressure, diabetes and serum cholesterol permits the identification of patients at high risk (>20% 5-year risk), whereas the use of serum cholesterol alone has a low gradient of risk, significantly poorer than the assessment of BMD alone to predict hip fracture [3,22].

Absolute Fracture Risk

Absolute risk, or more exactly ‘long-term probability’, has generally been calculated in the context of lifetime fracture risks. These probabilities take account not only of the incidence of fracture at different ages, but also of the likelihood that individuals with given characteristics at the time of assessment will survive. For long-term predictions, account needs to be taken of secular trends in mortality [23], which has been improving in all regions of the world [24]. Such estimates of lifetime probability of fracture are of value in considering the future burden of disease in the community and the likely effects of intervention strategies on the population. They are less relevant for assessing the risk in individuals in whom treatment might be envisioned. This is because treatments are not presently given for a lifetime, due variably to side effects, low compliance and cost. For shorter-term treatments, lifetime probabilities are inappropriate since the remaining lifetime risk for many fractures decreases progressively with age (Fig. 3) but the risk during treatment, i.e., the short-term risk (e.g., 10-year probability) increases with age [25]. Moreover, the feasibility of lifelong interventions has never been tested using either high-risk or global public health strategies [6].

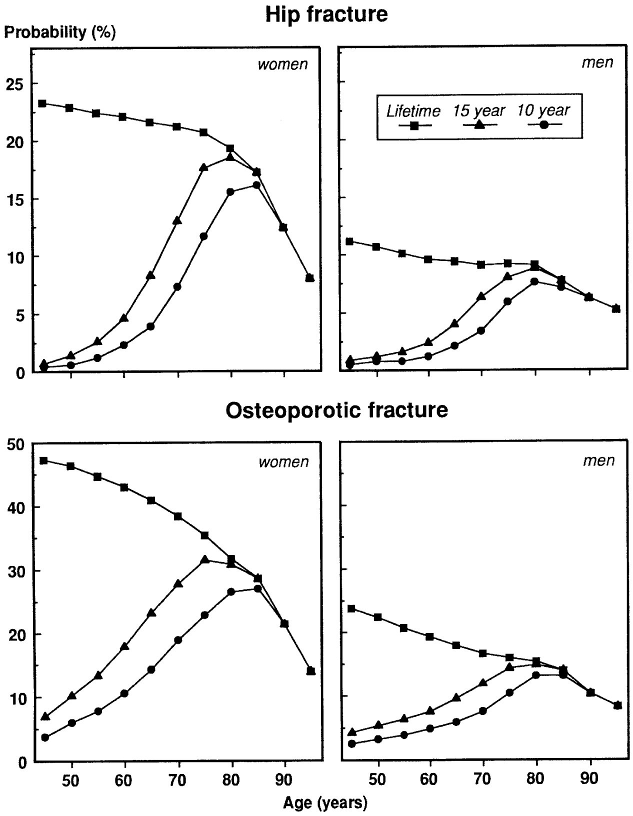

Fig. 3. Average long-term fracture probabilities in men and women from Malmö, Sweden for hip fracture alone and for hip, clinical vertebral, proximal humeral and distal forearm fractures combined [25].

For assessment of intervention strategies, a shorter time frame is appropriate, consistent with clinical practice. The optimal duration of treatments is not well evaluated, but interventions of 3–5 years or so correspond with information available from trials and models of the cost-effectiveness of treatment. For a number of treatments, effects on BMD appear to persist when treatment is stopped and there is some evidence that this may be true also for fracture risk [26]. The evidence for persistence of effect for several years after stopping treatment is greater for hormone replacement therapy (HRT), parathyroid hormone and the bisphosphonates than for calcium or vitamin D [26]. A 10-year time frame accommodates a treatment for 5 years with

Table 1. Ten-year probabilities (%) of a first fracture at the sites shown in men and women from Malmö by age [25]

Site of fracture	Age (years) 50		60		70		80		90	
	M	F	M	F	M	F	M	F	M	F
Distal forearm	1.2	3.9	1.7	5.6	0.9	7.2	1.4	7.3	0.1	4.3
Hip	0.8	0.6	1.2	2.3	3.4	7.3	7.6	15.5	6.2	12.4
Spine[a]	1.1	1.2	1.7	2.7	3.1	5.9	4.4	6.9	1.4	5.0
Proximal humerus	0.5	1.2	0.7	2.3	1.5	4.4	1.9	5.6	2.1	5.8
Any of these	3.3	6.0	4.9	10.6	7.6	18.9	13.1	26.5	10.3	21.4

[a] Clinically diagnosed fractures.

an offset of effect over the subsequent 5 years. Time frames in excess of 10 years may be misleading for patients considering treatment when the period of greatest fracture risk will occur far in the future when treatment has been stopped. Long time frames also pose problems in assessing the predictive value (odds ratio or relative risk) of risk factors that may decrease over time. Thus, theoretical calculations indicate that the long-term predictive value of BMD for fractures wanes with time due to variations in rates of bone loss, and this is substantiated by empirical observation [27,28]. The same may be true for other risk indicators, for example the ratio of carboxylated to total serum osteocalcin [29]. Against this background, 10-year probabilities seem appropriate. Ten-year probabilities of the common osteoporotic fractures for Swedish men and women of different ages are given in Table 1 [25].

The Choice of Fracture End-points

Hip fracture is the most important consequence of osteoporosis as judged by the mortality and morbidity experienced by patients and costs to health providers. However, intervention thresholds determined on the probability of hip fracture risk alone would neglect the many other fractures that occur, particularly in younger age groups where these other types of fracture predominate. Even over the age of 80 years, hip fracture represent less than 50% of all fractures [30,31]. Moreover, consideration of other fractures requires an evaluation not only of the site-specific pattern of fracture incidence with age, but also of their morbidity. Although less devastating than hip fractures, distal forerm fractures and vertebral fractures, for example, cause substantial impairment in the activities of daily living [32]. Thus, an intervention that prevented 5 fractures per 100 treated patients (number needed to treat; NNT = 20) would have a different significance at the age of 50 years when hip fractures are rare, than at the age of 70 years, when they comprise a much higher proportion of fractures.

A further consideration is that not all fractures are due to osteoporosis, for example fractures of the face and skull. Treatments may not affect the risk of this type of fracture. Thus, in the FIT trial, treatment with alendronate had less efficacy on appendicular fractures in women without osteoporosis [33]. A more recent example is the lack of effect of risedronate in elderly women selected by their risk of falling compared with those selected on the basis of low BMD [34]. In determining risk thresholds for pharmacologic interventions, account needs to be taken, therefore, of those fractures that are due to osteoporosis.

Osteoporotic fractures have been variously characterized on the basis of low-energy trauma, low BMD, rising incidence with age or associations with other osteoporotic fractures, but no approach is perfect [35,36–39]. An approach used recently is to characterize fractures due to osteoporosis as those (a) associated with low BMD and (b) where the incidence increases with age [40]. An alternative is for expert panels to assign the proportion of fractures at any one site that are due to osteoporosis [38,41,42], but this rests on as many assumptions. The responsivity of fracture risk to intervention may be a further useful approach when more data are available.

The many fractures that occur in osteoporosis pose problems for simplifying the assessment of risk because of the multiple outcomes (hip, vertebral, Colles' fracture, etc.) and the consequences of these fractures vary according to the site of fracture. An approach to resolving the problem is to weight different fractures according to the disutility (utility lost) from each type of fracture. Quality-adjusted life years (QALYs) are the accepted parameter in the health economic assessment of interventions [43] and can be used to calculate disutilities. In order to estimate QALYs, each year of life is valued according to its utility, which ranges from 0 (equal to death) to 1 (perfect health). The disutility associated with each fracture is the cumulative loss of utility over time. Disutility decreases with age due to the higher mortality. As expected, the disutility from different fractures varies, the greatest loss being from hip fracture. The 'exchange rate' is approximately 1 hip fracture for 4 vertebral fractures or 20 for less severe fractures such as Colles' fracture [40].

Adding all disutility-weighted osteoporotic fractures has a marked effect on intervention thresholds (Fig. 4). The left-hand panel in Fig. 4 shows the 10-year probability of hip fracture according to *T*-score at the hip and age in Swedish women [9]. If, for example, an intervention threshold were set at a 10-year probability of 15%, then women with osteoporosis (*T*-score <−2.5 SD) would fall within the threshold risk from the age of 65 years onwards. The right-hand panel includes the probabilities computed taking other osteoporotic fractures into account [40]. The same threshold risk is attained in women from the age of 57 years, Thus, this type of approach reduces fractures and their consequences to a common currency and permits the

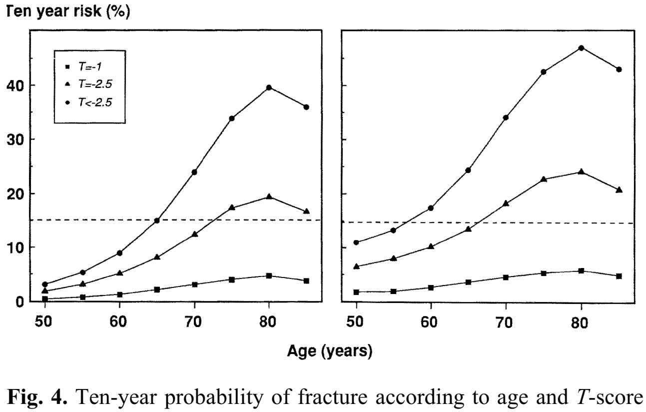

Fig. 4. Ten-year probability of fracture according to age and *T*-score at the hip in women from Sweden. The *left-hand panel* shows the probabilities for hip fracture. The *right-hand panel* shows probabilities adjusted to take account of fractures in addition to hip fracture. The *horizontal dotted line* denotes a hypothetical intervention threshold.

development of intervention thresholds that take account of the multiple outcomes of osteoporosis.

Ethnic and Geographic Applicability

The validity of this approach to other countries depends upon a commonality in the pattern of fracture incidence in different countries. One challenge is to take account of the large variation in fracture risks worldwide, which are best documented in the case of hip fracture. The incidence of hip fracture worldwide varies by more than 10-fold [44,45]. Many of these studies are from registers, but prospective studies also show a similar variation in risk [46]. There are also variations in the risk of other osteoporotic fractures, though those have been less well studied. In general, the available data suggest that the pattern of fracture is similar, i.e., in those countries where the risk of hip fracture is high then so too is the risk of forearm, vertebral and other osteoporotic fractures [31,36,40,47–49]. Thus, for any given age the ratio of hip to other fractures is relatively constant between countries, at least in the Western world (Fig. 5), and, where the hip fracture rate is known, the risks and consequences for other osteoporotic fractures can be estimated.

Over the long term, the probability of fracture depends not only upon fracture hazards, but also on mortality, and this too varies from country to country. Nonetheless, where mortality risks and hip fracture risks are known, 10-year probabilities of hip fracture can be computed. Some examples are given in Table 2. In general, where the probability is high in men, the probability is high in women, permitting hip fracture probabilities to be standardized to a reference country, e.g., Sweden [50]. On the assumption that other fractures can be computed from hip fracture rates, probabilities can be adjusted according to geographic location.

Table 2. Ten-year probability of hip fracture (%) in men and women according to age and country [50]

Country	Men aged (years)				Women aged (years)			
	50	60	70	80	50	60	70	80
USA (Rochester)	0.4	1.2	2.5	5.4	0.7	1.8	4.6	13.7
UK	0.2	0.7	2.0	4.6	0.3	1.3	4.3	12.9
Norway (Oslo)	0.6	2.1	4.7	10.5	1.2	2.4	7.8	13.0
France (Picardy)	0.4	0.7	1.2	2.1	0.3	0.8	2.1	6.2
Australia (Geelong)	0.4	0.5	2.3	5.6	0.2	0.9	4.7	14.8
China (Hong Kong)	0.3	1.0	2.4	4.9	0.4	1.2	4.6	9.6
China (Beijing)	0.2	0.7	0.9	1.9	0.2	0.6	1.1	1.9
Turkey (Istanbul)	0.1	0.2	0.6	1.0	0.1	0.3	0.5	1.0

Risk Factors

BMD measurements alone are not adequate to provide a sole instrument for population screening, but there are a large number of other risk factors that are consistently associated with fracture risk. Apart from age, sex and geographic location they include prior fractures, use of corticosteroids, low body mass index, biochemical markers of bone resorption and certain diseases associated with osteoporosis. Other putative risk factors

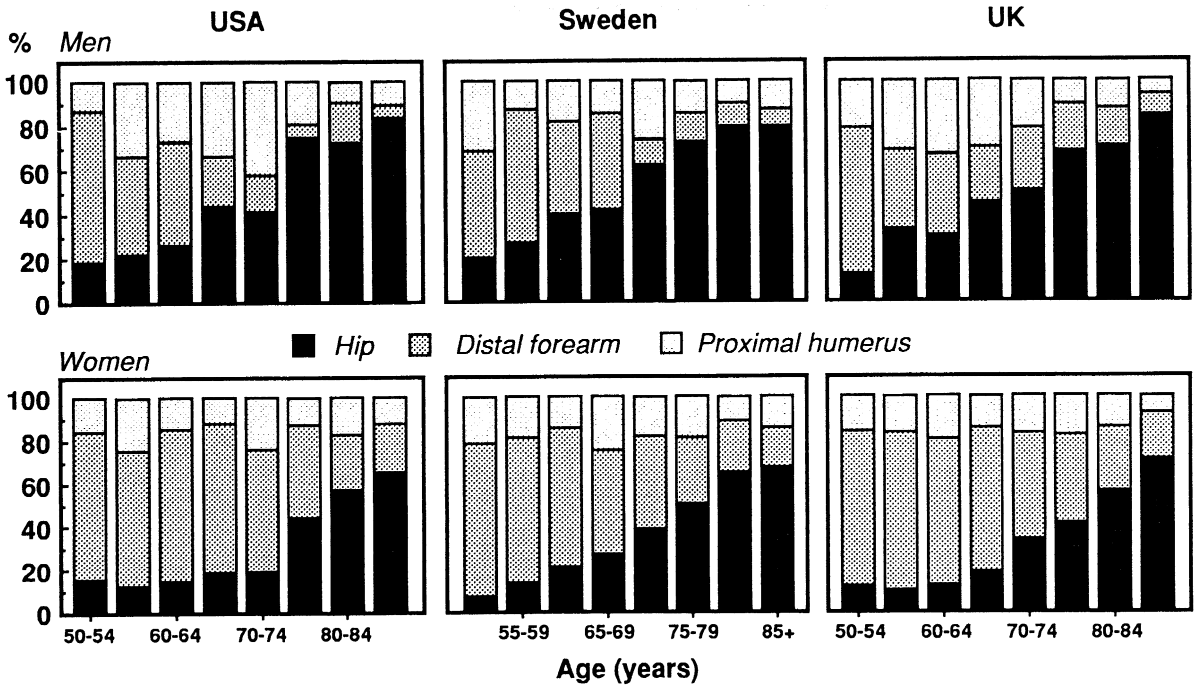

Fig. 5. Pattern of common osteoporotic fractures expressed as a proportion (%) of the total in the USA, Sweden and the UK. Data from the USA are from Melton et al. [31], Sweden from Kanis et al. [40] and the UK from Singer et al. [47].

such as family history of fracture and smoking require to be validated more widely. The importance of these risk factors differs. Some are more or less independent in that they predict fractures significantly when the one is adjusted for the other. For example, a maternal family history of hip fracture increases the risk of hip fracture two-fold [51], and the relative risk falls only to 1.9 when adjusted for BMD. Thus, this risk factor can be utilized to enhance risk assessment in conjunction with BMD. Other risk factors are more or less dependent, for example body mass index (BMI) and BMD in the elderly [52,53]. Thus, either BMI or BMD can be utilized to characterize risk, but their use may be mutually exclusive. A third category of risk factors are partially dependent. An example is cigarette smoking and BMD. Among elderly women in the SOF study, hip fracture risk was increased 1.9-fold by smoking, but only by 1.3-fold when adjusted for BMD [10]. The combined risk is therefore not much greater than the risk associated with either factor alone. Thus, risk factors other than age or BMD can be used to identify patients in whom densitometry is indicated or to enhance the value of BMD.

There are, however, several considerations in the selection of risk factors for use in fracture prediction. First, different risk factors have different relevance at different ages. For example, an early menopause is a significant risk factor for any osteoporotic fracture in perimenopausal women [54], but is of uncertain significance for fracture in the elderly. Conversely, a family history of hip fracture appears to be a risk factor in the elderly but is not a consistent risk factor at menopause. Different risk factors may also have different relevance for different fracture sites. These may in part be due to the different pattern of fracture with age (e.g., hip fractures are common in the elderly). For example, high BMI and smoking are risk factors for ankle fractures but these factors do not contribute significantly to the risk of forearm fractures at the same age [54]. For forearm fractures low BMI and early menopause are important factors. It is thus evident that guidelines based on risk factor assessment need to take account of age and the distribution of fracture types that varies with age. In addition, age itself is a dominant risk factor, so that risk needs to be categorized by age since, if not, age dominates all assessments.

Clinical risk factors to be used for fracture prediction need to be chosen with care. They should be:

- Validated in multiple populations
- Adjusted for age, sex and type of fracture
- Readily assessable by primary care practitioners
- Contribute to a risk that is amenable to the therapeutic manipulation intended
- Intuitive rather than counterintuitive to medical care.

An example of the last point is dementia, which carries a very high risk of hip fracture in men and women. Physicians might, however, be reluctant to target osteoporosis treatments on the diagnosis of dementia.

These considerations are important because guidelines should have a utility even where clinical risk factors alone are available for assessment. In other settings, bone mineral measurements make an important contribution to fracture risk prediction. Emphasis to date has been on measurements by dual-energy X-ray absorptiometry (DXA) at the hip, but guidelines should accommodate measurements by peripheral devices including validated ultrasound technologies, since they are reimbursed in many countries such as the USA. Similarly, they should incorporate other laboratory-derived risk factors such as biochemical tests and other skeletal measurments where these are known to contribute significantly to fracture risk. A final consideration in the context of intervention thresholds is to ensure that the risk identified can be modified by the intended intervention, so that the focus needs to be on the assessment of ‘preventable risk’.

Risk Assessment

Although BMD at the hip predicts hip fracture as well as blood pressure predicts cardiovascular disease [22,55], neither technique is adequate for population screening. For example, if it were wished to select for treatment the 15% of the female population at highest risk at the menopause (Table 3), the use of hip BMD would have a specificity of 85% but a sensitivity of only 45% [15]. The low sensitivity indicates that the majority of fractures (55%) would occur in those women categorized as being at low risk. With a technique with a poorer gradient of risk, for example 1.5 per 1 SD change, the sensitivity falls to 27%. Thus, 73% of fractures are missed for comparable specificity. Fortunately, the combination of a continuous variable (e.g., BMD) and a dichotomous variable (e.g., prior fragility fracture) yields a continuous variable with a higher gradient of risk than the continuous variable alone. This has a marked impact on the detection rate (see Table 3). Gradients of risk exceeding 3.0 per SD have sensitivities of >50% in the example used above.

These considerations indicate that risk assessment should be based on an estimate of fracture probability derived from a panel of risk factors, the weight of each being categorized by age (i.e., age and fracture pattern), strength of predictive value and independence. The weighting can be based on the combined relative risks adjusted to the population by age. The use of the population risk as a reference is appropriate since the objective of risk assessment is to identify individuals at high risk compared with the general population. The adjustment of relative risk in this way applies to continuous variables as well as dichotomous variables. For example, a *Z*-score of -1 for BMD at the hip has a relative risk for hip fracture of 2.6 compared with individuals with an average BMD for age but a relative risk of 1.87 compared with the general population [15]. Similarly, a dichotomous risk factor should be adjusted to the population risk according to its prevalence at each

Table 3. Estimates of positive predictive value (PPV), sensitivity and specificity of measurements to predict hip fracture over 15 years or to death in women aged 50 years (a) or 65 years (b), according to different population cut-offs to define a high-risk category [15]

Gradient of risk	High-risk category (% of population)											
(RR/SD)	5			10			15			25		
	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)
(*a*) *Women aged 50 years*												
1.5	2.8	11.0	95.1	2.3	18.3	90.1	2.2	26.5	85.1	1.9	38.0	75.2
2.0	4.4	17.1	95.2	3.4	26.6	90.2	3.1	36.4	85.3	2.5	48.8	75.3
2.5	5.9	23.1	95.2	4.3	34.0	90.3	3.8	44.5	85.4	2.9	57.1	75.4
3.0	7.2	28.5	95.3	5.1	40.3	90.4	4.3	51.1	85.5	3.2	63.4	75.5
4.0	9.5	37.3	95.4	6.3	49.8	90.5	5.1	60.6	85.6	3.6	71.5	75.6
5.0	11.1	43.7	95.5	7.1	56.0	90.6	5.6	66.1	85.7	3.8	75.4	75.6
6.0	12.2	48.0	95.6	7.6	59.8	90.6	5.8	69.0	85.7	3.9	77.0	75.7
(*b*) *Women aged 65 years*												
1.5	15.7	10.5	95.4	13.2	17.7	90.6	12.8	25.7	85.9	11.1	37.0	76.0
2.0	23.3	15.6	95.9	18.4	24.7	91.2	17.0	34.1	86.5	13.9	46.4	76.7
2.5	29.7	19.9	96.2	22.6	30.2	91.6	20.1	40.4	87.0	15.8	52.8	77.2
3.0	34.6	23.2	96.5	25.6	34.3	92.0	22.3	44.8	87.4	17.0	56.9	77.6
4.0	41.3	27.6	96.8	29.4	39.4	92.4	24.7	49.7	87.8	18.1	60.6	77.9
5.0	44.8	30.0	97.0	31.1	41.7	92.6	25.6	51.4	87.9	18.2	60.8	77.9
6.0	46.7	31.3	97.1	31.7	42.5	92.6	25.6	51.4	87.9	17.8	59.5	77.8

Table 4. The effect of risk factors alone or in combination on the relative risk of hip fracture in women at the age of 80 years. The right-hand column gives the probability of hip fracture within the next 10 years [59]

Risk factors	Threshold values	Prevalence (%)	Risk ratio	Relative risk[a]	Ten-year probability (%)
Average	–	100		1.0	18.0
Low BMD	*T*-score <-2.5	56	2.8	1.40	23.6
Prior fracture	Yes	39	3.5	1.77	28.8
High CTX	Above premenopausal values	23	2.4	1.82	29.5
Low BMD + prior fracture	As above	23	4.1	2.39	36.3
Low BMD + high CTX	As above	16	4.1	2.74	40.1
Prior fracture + high CTX	As above	12	5.3	3.50	47.3

[a] Adjusted to the population.

CTX, carboxy-terminal crosslinked telopeptide of type I collagen.

age band. An example is provided by poor visual acuity. In the EPIDOS study poor acuity (<2/10), found in 7.3% of the population, was associated with a two-fold higher risk of hip fracture than better visual acuity (OR = 2.0) [56]. The increase in risk compared with the general population is

$$OR/P\ (OR + (1 - P)) = 1.86$$

Where P is the prevalence and OR the odds ratio. Thus, in this example the combined risk of low BMD ($Z = -1$ SD) and poor visual acuity is $1.86 \times 1.87 = 3.06$ compared with the risk for the general population [15]. Further examples of combinations of risk factors from the EPIDOS study [57,58] are given in Table 4 together with 10-year hip fracture probabilities applied to the Swedish population [59].

The selection of patients with risk factors that provide a high gradient of risk increases sensitivity, i.e., the detection rate of the test, without trading off specificity over a wide range of assumptions. This not only improves the detection rate, it also enlarges the population that can be selected with a given threshold of relative risk. Conversely, the lower the gradient of risk, the fewer the patients identified above any given threshold of risk. If, for example, it were intended to

Table 5. The effect of gradient of risk for fracture prediction (RR/SD) on the proportion of the population identified according to the threshold of relative risk [60]

RR/SD	Population RR					
	1.0	2.0	3.0	4.0	5.0	6.0
2.0	36.4	8.9	2.7	0.9	0.4	0.2
2.5	32.3	11.2	4.9	2.4	1.3	0.8
3.0	29.1	11.9	6.1	3.5	2.2	1.5
3.5	26.6	11.9	6.6	4.2	2.8	2.0
4.0	24.4	11.6	6.9	4.5	3.2	2.4

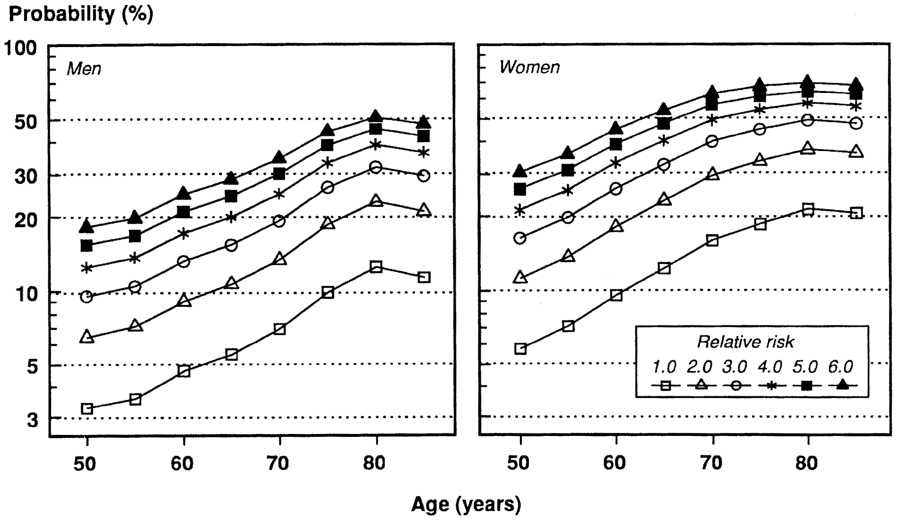

Fig. 6. Ten-year probability (%) of an osteoporotic fracture (hip, distal forearm, proximal humerus or clinical vertebral fracture) in men and women from Sweden according to age and relative risk [61].

identify individuals from the general population with a risk of 3 times higher or more than average, a test with a gradient of 2.0 per SD would identify 2.7% of the population, but a test with a gradient of risk of 3 per SD would detect 6.1% of the general population. Other examples are provided in Table 5 [60]. The general relationship between relative risk and fracture probability is shown in Fig. 6 [61].

Intervention Thresholds

The objective of assessment is to provide information that can be used for decision-making in the management of patients. There are broadly three decisions that can be based on fracture probability. The three decisions are:

- No further assessment or treatment required
- Further assessment indicated, e.g., diagnostic assessment
- Treatment indicated irrespective of any diagnostic assessment.

Note that DXA at the hip is considered to be the diagnostic test for osteoporosis. However, the threshold of BMD for intervention will vary according to the risk factor profile including the risk contributed by age. In this sense BMD is utilized as a risk assessment, since in many instances intervention thresholds will be less stringent than the diagnostic threshold.

The choice of a probability threshold for each decision point is complex and depends upon not only absolute risk, but the efficacy of interventions and their costs. Health economic justifications, based on cost-effectiveness, result in thresholds for each intervention, because they will vary according to costs and efficacy [10]. However, there are obvious arguments for not providing separate thresholds for each treatment available in each country at each cost. Not only is this complexity unwieldy, but practitioners first decide whom to treat and only thereafter consider the method of treatment, and not vice versa. Although it is likely that effectiveness and side effects of interventions differ, there is inadequate evidence to provide a hierarchy of treatment based on effectiveness [6]. It is considered, therefore, that guidelines should focus on developing a standard intervention and assessment threshold irrespective of the intervention intended. One approach is to determine cost utility with a basket of treatments of average cost and effectiveness. This approach does not accommodate agents that have significant extraskeletal benefits and risks such as HRT or the SERMs. The argument for not providing different thresholds is that they evolve guidelines towards product specificity. The argument for their provision is that cost-effectiveness is critically dependent on these extraskeletal risks and benefits. For example, a significant reduction of breast cancer risk with treatment in women with osteoporosis would mean that it would be cost-effective to treat women with a lower (less stringent) probability threshold than with a treatment without this effect.

Summary and Conclusions

The diagnosis of osteoporosis is made from the measurement of BMD. DXA at the hip is the appropriate diagnostic site. Current clinical guidelines follow the principle that BMD measurements are indicated in individuals with risk factors for fracture and that treatment is recommended in those with a BMD below a critical value. In some countries reimbursement for the costs of treatment depend upon such thresholds for BMD. In Europe the critical value corresponds to a T-score of -2.5 SD, whereas in the USA less stringent criteria are used. It is evident, however, that fracture risk at any given T-score varies markedly according to age and other risk factors. This has led to the view that interventions should be targeted to those at high risk, irrespective of a fixed BMD threshold. In this sense, BMD is utlized as a risk assessment, since in many instances intervention thresholds will be less stringent than the diagnostic threshold. Thus, intervention thresholds need to differ from diagnostic thresholds and be based on fracture probabilities. A 10-year fracture probability appears to be an appropriate time frame.

There are a number of problems to be overcome in the development of assessment guidelines. They need to take account of not only the risk of hip fracture but also that of other fractures which contribute significantly to morbidity, particularly in younger individuals. A promising approach is to weight fracture probabilities according to the disutility incurred compared with hip fracture probability. Account also needs to be taken of the large geographic variation in fracture probabilities worldwide. A further challenge for the future will be to identify risk factors that predict fracture with high validity in different regions of the world and their independent contributions, so that models of risk prediction can be constructed and ultimately validated in independent cohorts.

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