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EDITORIAL

Population screening for fracture risk in postmenopausal women — a logical step in reducing the osteoporotic fracture burden?

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Introduction

Systematic approaches to improving the management and treatment of patients with osteoporotic fractures are increasingly advocated in many countries. One example, outlined by the Department of Health in the UK in 2009, presented a stratified approach, firstly recognizing the need to provide optimal care to those with hip fractures, followed by the provision of services that would identify, investigate and treat those presenting with non-hip fragility fractures (Fig. 1). A standardized approach to post hip fracture care published in 2007 [1] was followed by a reduction in 30-day mortality, falling by 7.6% per year in the 4 years after the introduction of a National Hip Fracture Database compared to a 1.8% per year decrease in the 4 years preceding its introduction [2]. Similar systems are being established in other countries [3, 4].

Improved management of those presenting with non-hip fractures is also addressed through the establishment of Fracture Liaison Services (FLS), usually via a hospital-based coordinator to identify patients aged 50 years and over with a fracture [5, 6]. To date, evidence has shown increased DXA testing, treatment initiation and early adherence in FLS-like settings [7–10]. Some observational studies have shown reductions in fracture risk, though interpretation is complicated by inherent biases in some though not all studies [10, 11]. The number and standard of FLS worldwide continue to increase under the auspices of the International Osteoporosis Foundation's Capture The Fracture program (https://www.capturethefracture.org/).

Nonetheless, many patients with past fractures remain unidentified and so untreated, and contribute to a large pool of patients in the general community at high risk of fragility fracture (see Fig. 1). Here, the burden of osteoporosis assessment and management goes to primary care, but the biggest barrier to effective reduction in fracture rates remains the low awareness of osteoporosis amongst primary care physicians leading to marked under-identification of high-risk patients and low treatment rates worldwide [12–16]. The large and increasing treatment gap raises the question if it is now time to consider systematic approaches for the identification of high fracture risk in the wider primary care setting, including the establishment of population screening or enhanced case-finding programs.

In 2019, two reviews concluded that screening for osteoporosis could not yet be supported or recommended [17, 18]. Both recognized, however, that the ability of screening to reduce hip fracture risk had some potential and since then a meta-analysis of three prospective, randomized controlled studies of FRAX-based screening has shown a significant reduction in hip fractures [19]. Whether or not osteoporosis, or more specifically high hip fracture risk, fulfils the criteria for screening has been addressed in a recently published position statement from the Epidemiology/Quality of Life Working Group (Epi/QoL WG) of the International Osteoporosis Foundation [20]. This editorial summarises the key issues relating to the proposed screening program.

Several specific characteristics of a proposed screening program for diseases are important to consider [21]. These

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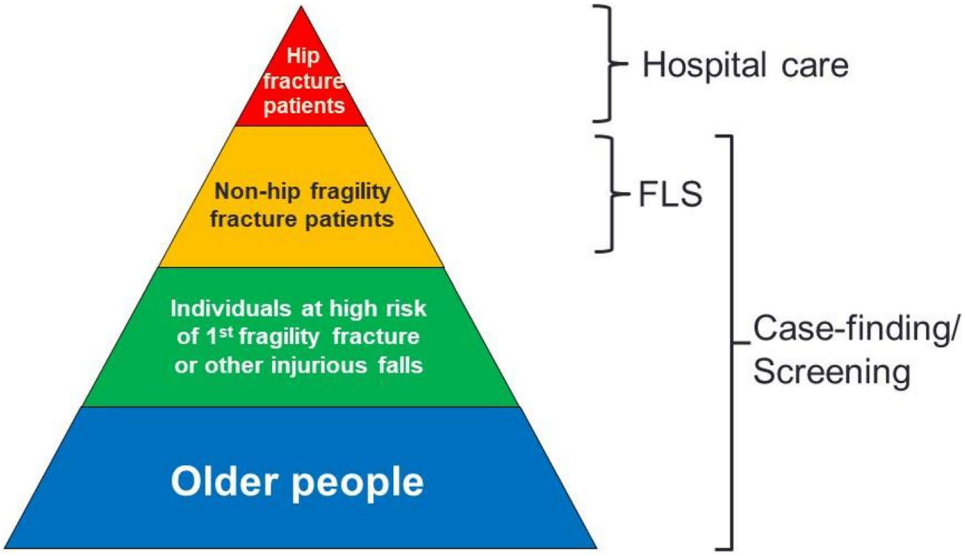

Fig. 1 A systematic approach to fracture prevention adapted from that outlined by the Department of Health in the UK. FLS – Fracture Liaison Services. A. Outcome—Hip fracture. B. Outcome – Major osteoporotic fracture

include whether the target population is sufficiently large to enable safe, clinically and cost-effective screening, and whether effective means exist of identifying, contacting and informing the whole target population. The subsequent formal assessment of the evidence for screening covers the key issues relating to the condition, the test, the treatment and the effectiveness of any proposed screening program.

The proposed screening program

The strategy is based on that examined in the Screening for Osteoporosis in Older People (SCOOP) study in the UK [22–26]. In brief, a risk factor questionnaire based on the FRAX® risk assessment tool would be completed, in paper form or electronically, by women age 70 years or older through self-completion, with family or caregiver assistance if needed. Those with low hip fracture probability would receive a letter of reassurance with general lifestyle advice, whilst the remainder would have an additional assessment of femoral neck bone mineral density using local densitometer facilities. The bone density result would then be incorporated in an updated FRAX calculation, and those that have hip fracture probabilities above an intervention threshold would be recommended for treatment. The recommendation would be communicated to both the individual and their primary care physician. A similar approach could be undertaken in those countries with a hip fracture risk comparable to or higher than that in the UK [27].

The age threshold (70 years) reflects the need to identify for a suitably high-risk group to ensure that the program would have good clinical and cost effectiveness (vide infra).

The condition

Osteoporotic fractures are undoubtedly a common public health problem [28–31]. The incidence of fragility fractures increases markedly with age; hip fractures are relatively rare at the age of 50 years but become the predominant fracture from the age of 75 years[32].

In 2019, 4.3 million new fragility fractures were estimated to have occurred in the EU, of which approximately 827,000 were hip fractures [30]. Approximately half of the 248,487 deaths causally related to fractures were attributable to hip fractures. The cost of osteoporosis, including pharmacological intervention was estimated at €56.9 billion, with two-thirds derived from the treatment of fractures and only 3% representing the costs of pharmacological intervention. The management and consequences of hip fractures represented 54% of these costs.

The epidemiology and natural history of osteoporotic fractures, particularly hip fractures, are well documented, with a number of easily collected risk factors that can be identified prior to the occurrence of fracture. Currently, the detection of osteoporotic bone mineral density (BMD) is a recognised tool for screening for fracture risk in some countries (e.g. the US), but its low sensitivity (i.e. the majority of osteoporotic fractures occur in individuals with BMD values above the osteoporosis threshold) [33] has precluded it from being accepted as a public health screening test in many countries to date [34, 35]. A huge body of evidence on other 'non-BMD' risk factors has been published over the last 30 years and has contributed to the development of fracture risk assessment tools.

The test

The increasing recognition and acceptance that treatments for osteoporosis should be targeted on the basis of fracture risk requires well-validated assessment tools providing ease of use in clinical practice. Of these, the FRAX tool has achieved widespread use with incorporation into numerous guidelines worldwide, and a large number of studies evaluating its utility [36–43]. Most importantly, in the context of screening, FRAX is currently the only fracture risk assessment tool to be studied until now in randomised, controlled studies of population-based screening.

For women age 70 years and above, the intervention threshold set by the National Osteoporosis Guideline Group (NOGG) is a MOF 10-year probability of 20% (or a hip fracture probability of 4.8%). The threshold is set to be equivalent to that of a woman age 70 years with a prior fragility fracture. Assessment thresholds, between which a BMD test would be undertaken to refine the probability assessment, lie between 11 and 24%. In principle, a similar approach could be used in other high-risk countries as shown in Table 1. In practice, intervention thresholds are most appropriately determined at regional or national levels, given that each health care system will consider local/national factors such as reimbursement issues, health economic assessment, willingness to pay for health care in osteoporosis, and access to dual-energy X-ray absorptiometry (DXA).

The treatment

Of the many factors that influence the risk of fracture, age-related reductions in bone mass and increased likelihood of falling are important contributors [44]. While assessment of falls risk and appropriate interventions aimed at reducing falls risk have been shown to be effective [45], at least in the short term, their impact on the risk of fracture, particularly at the hip, is less certain [46–48]. In contrast, many randomised, placebo-controlled trials have shown that treatments directed at maintaining or improving bone mass can significantly reduce the incidence of fracture at vertebral and non-vertebral sites including the hip [49–52]. Recent comparative clinical trials have provided evidence of enhanced anti-fracture efficacy of anabolic compared with antiresorptive therapies [53, 54], prompting considerations of starting treatment with an anabolic agent in patients at very high risk of fracture as a more appropriate means of rapidly reducing fracture risk [16, 55, 56].

Several randomised, controlled studies have also demonstrated the benefit of osteoporosis interventions in populations unselected for BMD-defined osteoporosis. For example, in the Women's Health Initiative study, the 34% reduction in hip fracture risk by menopause hormone therapy in women age 50–79 years with an intact uterus was independent of baseline BMD [57, 58]. A similar BMD-independent effect on fracture risk reduction was observed in a 3-year randomised, placebo-controlled study of the oral bisphosphonate, clodronate, in women age 75 years and older, again unselected for osteoporosis [59]. In contrast, a post hoc analysis demonstrated that treatment with clodronate was more effective in women at higher baseline major osteoporotic fracture risk assessed by the FRAX tool [60]. Finally, that osteoporotic BMD is not required for fracture reduction was more recently demonstrated in a study of 18-monthly infusions of zoledronate in women age 70 or older with BMD-defined osteopenia [61].

Table 1 Possible threshold values of FRAX 10-year probabilities of major osteoporotic (MOF) and hip fractures in women with prior fracture at the age of 70 years in the UK and examples of some other high-risk countries if adopting the same approach (ranked in descending order of hip fracture probability) (Body mass index set to 25 kg/m^2)

Country	MOF probability Threshold	Hip probability Threshold
Denmark	28%	8.8%
Sweden	25%	8.7%
Norway	22%	7.4%
Singapore (Chinese)	19%	6.0%
USA (Caucasian)	21%	5.0%
UK	20%	4.8%
Canada	19%	4.4%
Japan	18%	3.9%

Effectiveness of the screening program

The proposed screening program is based on the randomised, controlled SCOOP study [23]. Two additional randomised studies, namely the Risk-stratified Osteoporosis Strategy Evaluation study (ROSE) from Denmark [62] and the SALT Osteoporosis Study (SOS) from the Netherlands [63], have also used FRAX-based approaches for population screening. The design and screening approaches used in these trials have been published previously and are outlined in Table 2.

Overall, of the screened women in each of the studies, the proportion identified as requiring treatment was similar in ROSE (13.3%) and SCOOP (14.4%), but was higher in SOS (25%).

Bearing in mind the relatively small proportions recommended for treatment, none of the three studies individually showed a significant overall reduction in the incidence of osteoporotic fractures, but a meta-analysis of all three studies showed a small but significant 5% reduction (HR 0.95,

Table 2 Comparison of screening strategies across the SCOOP, ROSE and SOS studies in women

	SCOOP	ROSE	SOS
Age range	70–85 years	65–80 years	65–90 years
Number recruited (with baseline FRAX if different)	Control 6250 Screening 6233	Control 17,157 (9326) Screening 17,072 (9279)	Control 5457 Screening 5575
1st Screening step			
Assessment	FRAX 10-year hip probability without BMD	FRAX 10-year MOF probability without BMD	FRAX 10-year MOF probability with BMD (plus VFA)
Definition of positive test	Probability ≥ age-dependent assessment threshold	Probability ≥ 15% or more	See treatment criteria below
2nd Screening step			
Assessment	DXA measurement of BMD	DXA measurement of BMD	N/A
Treatment criteria	Probability (with BMD) ≥ age-dependent intervention threshold	BMD T-score ≤ -2.5	Probability ≥ age-dependent thresholds + BMD T-score ≤ -2, or a prevalent vertebral fracture, or met criteria within Dutch guidelines
Performance per prevented fracture			
NNS/NNT (Ost fracture)	133/19	319/34	178/32
NNS/NNT (Hip fracture)	115/17	281/30	552/98

95%CI 0.89–1.00) [19]. When the analysis was confined to major osteoporotic fractures, screening resulted in a 9–10% significant decrease (Fig. 2B) [20]. More importantly, the largest impact of the three studies combined was on the rate of hip fractures; again bearing in mind the relatively small proportion treated, the meta-analysis showed a 20% reduction (HR 0.80, 95%CI 0.71–0.91) in hip fractures (Fig. 2A) [19]. In the pooled cohorts, the numbers needed to screen (NNS) and treat (NNT) for hip fractures were 272 and 28 respectively. The meta-analysis clearly showed population screening to be effective, with the biggest reduction observed in the outcome of hip fracture, leading the authors to conclude that implementation of screening in older women should be considered a serious option.

Several cost-effectiveness analyses of potential population screening strategies in osteoporosis have been published over the last 20 years, but relatively few have been tested in randomized controlled trials [64–66]. Of the three recent randomised controlled studies using FRAX, only the SCOOP study has published cost-effectiveness analyses to date. A recent analysis using a well-established health economic Markov model study design, and populated with costs derived from the SCOOP study, was found to be cost-saving. The analysis reported that for every 1000 women screened, 9 hip fractures and 20 non-hip fractures would be saved over the remaining lifetime (mean 14 years), with a cost reduction or saving of £286 in comparison to usual management. Thus, the opportunity costs of the screening program are low or even cost-saving, and are comparable to or better than many public health measures [67] or other established screening programs [68, 69].

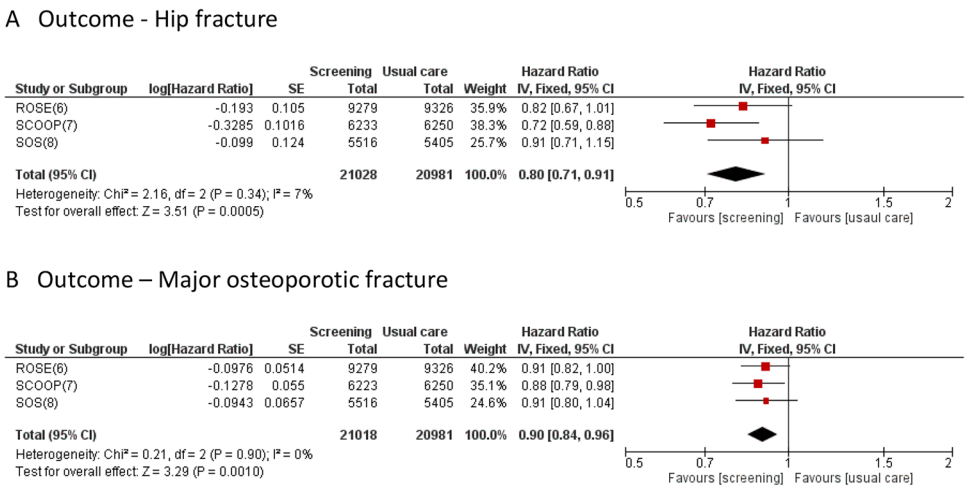

Fig. 2 Forest plots of screening for prevention of hip (2A, adapted from [19]) and major osteoporotic (2B) fractures versus usual care. Note: From the ROSE study, the data from the first per protocol analysis were used, as these were most comparable to the data from the SCOOP and SOS studies. In Fig. 2B, the meta-analysis from [19] has been updated to include the major osteoporotic fracture outcome from the SCOOP study

Conclusion

The IOF EpiQOL Working Group has recently assessed the potential of a program that screens for high hip fracture risk in the community against criteria set by the UK National Screening Committee. In this editorial, we have summarized the performance of the proposed screening program against the four established key criteria of condition, test, treatment and effectiveness. We would contend that a program based on self-reported assessment of FRAX 10-year probability of hip fracture with subsequent measurement of femoral neck BMD where appropriate, and treatment with licensed treatments predominantly oral bisphosphonates, fulfils these criteria. The data considered here and conclusions drawn should be of value in many healthcare settings, and research should now focus on strategies for optimal implementation of this approach. Transitioning towards screening to improve identification of hip fracture risk in older women in primary care (e.g., enhanced case-finding) will also have a positive impact on the burden of this most serious of osteoporotic fractures.

Declarations

Conflicts of interest E.V.M reports consultant/advisor fees, speaker honoraria and or, research funding from AgNovos, Amgen, Consilient Healthcare, Fresenius Kabi, Gedeon Richter, Internis, Lilly, Novartis, ObsEva, Synexus, and UCB, all outside the submitted work.

Ethics approval and consent to participate This narrative article contains no original data and thus issues of ethics, informed consent and patient confidentiality do not apply.

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C.C. reports personal fees from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work.
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M.L. reports lecture fees from Amgen, Astellas, Lilly, Meda, Renapharma, and UCB Pharma and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma, and Consilient Health, outside the submitted work.
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J. A. reports grants and personal fees from Amgen outside the submitted work, grants from Radius and has been an advisor to Gilead and is part of their speaker's bureau, outside the submitted work.
F.B. is employed and is a shareholder in Quantify Research, a health economic research consultancy, outside of the submitted work.
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All other authors have no relevant conflicts of interest in relation to the submitted work.

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