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Position Development Paper

Official Positions for FRAX® Clinical Regarding Falls and Frailty: Can Falls and Frailty be Used in FRAX®?

From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®

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Abstract

Risk factors for fracture can be purely skeletal, e.g., bone mass, microarchitecture or geometry, or a combination of bone and falls risk related factors such as age and functional status. The remit of this Task Force was to review the evidence and consider if falls should be incorporated into the FRAX® model or, alternatively, to provide guidance to assist clinicians in clinical decision-making for patients with a falls history. It is clear that falls are a risk factor for fracture. Fracture probability may be underestimated by FRAX® in individuals with a history of frequent falls. The substantial evidence that various interventions are effective in reducing falls risk was reviewed. Targeting falls risk reduction strategies towards frail older people at high risk for indoor falls is appropriate. This Task Force believes that further fracture reduction requires measures to reduce falls risk in addition to bone directed therapy. Clinicians should recognize that patients with frequent falls are at higher fracture risk than currently estimated by FRAX® and include this in decision-making. However, quantitative adjustment of the FRAX® estimated risk based on falls history is not currently possible. In the long term, incorporation of falls as a risk factor in the FRAX® model would be ideal.

Key Words: Falls; fracture; FRAX; sarcopenia; frailty.

Introduction

The World Health Organization fracture risk assessment tool (FRAX®) algorithm has been developed to estimate the 10-year risk of hip and major fractures based on clinical risk factors, with or without bone mineral density (BMD). The risk factors included in FRAX are: age, sex, body mass index (BMI), personal history of fracture, parental history of hip fracture, current smoking, alcohol intake, glucocorticoid use, rheumatoid arthritis, other causes of secondary osteoporosis and with the option of including femoral neck BMD. Risk factors identified for hip fractures can either be purely skeletal related such as bone mass, bone geometry, bone microarchitecture, bone turnover, or be fall related such as neuromuscular function, cognitive impairment, visual acuity, certain medications, or can be both skeletal and fall related such as age, genetic factors, family history of fracture, weight, weight change and mobility *(1)*. One criticism of the FRAX model by some users has been the lack of consideration of falls or falls risk in predicting fractures.

The remit of this FRAX Clinical Task Force Sub-Committee is to review the evidence and consider if falls

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should be incorporated into the FRAX model or alternatively provide guidance to clinicians on how a history of falls should be used in conjunction with FRAX in their clinical decision-making.

Methodology & Data sources

A Medline search was conducted using ''falls'' and ''fractures'' and ''fracture prediction'' as search terms. This search was limited to the English language. Relevant citations were included at the discretion of the task force members.

Statements

***Question*:** Should a falls history be incorporated into FRAX?

***Official Position*:** *Falls are a risk factor for fractures but are not accommodated as an entry variable in the current FRAX model. Fracture probability may be underestimated in individuals with a history of frequent falls, but quantification of this risk is not currently possible.*

***Grade*:** Good, A, W

***Ad hoc Task Force Opinion not Approved by the Expert Panel*:** Existing data are not of adequate quality to incorporate quantitative adjustment to FRAX at the present time. As such, *it is recommended that FRAX users be made aware that non-consideration of falls (especially recurrent falls) is likely to underestimate 10 year fracture risk. Moreover, it is suggested that advice regarding qualitative adjustment of fracture risk be provided.* To this end, the following text is suggested: ''Data from the Study of Osteoporotic Fractures suggest that, in comparison to individuals without a fall in the previous year, a history of each fall (up to 5 falls or more) in the previous year increases the 10 year hip fracture risk by approximately 30 % in women.''

Rationales

In the future, a falls history should be incorporated into FRAX. At this time, it is recommended that FRAX users be made aware that FRAX currently underestimates fracture risk in patients with falls. As an example, an accompanying statement could be added to FRAX as follows: ''Data from the Study of Osteoporotic Fractures suggest that in comparison to individuals without a fall in the previous year, a history of each fall (up to 5 falls or more) in the previous year increases the 10 year hip fracture risk by approximately 30 % in women.'' Such an approach would allow the FRAX user, if they wished, to adjust the 10-year fracture risk estimates.

Based on the above, falls clearly contribute to fracture risk and therefore, their exclusion from FRAX leads to underestimation of the actual 10-year risk. While classical osteoporosis therapies, e.g., bisphosphonates, do not reduce falls risk, other current, and potential future, approaches do reduce these risks. As fracture reduction is the ultimate goal of ''osteoporosis'' therapy, inclusion of falls into the FRAX algorithm, and subsequent clinical interventions to reduce falls risk, will lead to further reduction of fractures.

Discussion

Epidemiology of Falls and Relationship Between Falls and Fractures

Falls are common amongst older people and a major public health concern in terms of morbidity/quality of life, mortality and cost to the health and social services. The prevalence has been estimated as 28−35% in community dwelling older people aged 65 years and up to 42% in those aged over 75 years *(2)*.

Around 40−60% of falls in older adults lead to injuries, with 30−50% resulting in minor trauma, 10−15% lead to serious injuries with around 5−10% resulting in fracture, 1−2% of these being hip fractures. Older people with injuries following falls are found to have a subsequent increase in institutional care, decline in functional status and increased use of medical services *(2)*. Fear of falling is well recognised in older people and causes activity limitation and anxiety. Associations include living alone, cognitive impairment, depression, and balance and mobility impairments *(3)*. One study showed up to 60% of community dwelling older adults reported moderate activity restriction due to fear of falling *(4)*. The importance of preventing falls was highlighted in a study which found 80% of older women preferred death to a bad hip fracture resulting in nursing home admission *(5)*.

As in all major geriatric syndromes, multiple risk factors are involved in falls with chronic predisposing and acute precipitating factors and interactions playing a crucial role *(6)*. Older persons with limited functional reserve, i.e., a precarious physiological and physical balance, have the potential to fall from seemingly minor physiologic, intrinsic and/or extrinsic risk factors; and the greater the number of risk factors the greater the risk for falls *(7)*. The most important intrinsic risk factors are: previous falls, decreased muscle strength (upper or lower extremity), gait and balance deficits, dizziness and orthostasis, visual impairment, depression, functional and cognitive impairment, low body mass index, urinary incontinence, chronic musculoskeletal pain, female sex and being 80 years and older. Interactions between medications (e.g. polypharmacy), psychotropic medications, and environmental risks (e.g. loose rugs, insufficient lighting) have been identified as major extrinsic risk factors *(8−10)*. Importantly, fear of falling is not only a consequence of falling as noted above, but also an important psychological risk factor for falls.

Most interventions have focused on trying to ameliorate these deficits and on making the home environment less hazardous. It is worth noting that risk factors for indoor and outdoor falls differ and mostly in opposite directions. Risk factors for indoor falls included older age, being female, and various indicators of poor health. Risk factors for outdoor falls included younger age, being male, and being relatively physically active and healthy. Combining these falls, as is done in many studies, masks important information. As most geriatric falls occur indoors, prevention recommendations for non-institutionalized older people should be more effective if targeted differently for frail, inactive older people at high risk for indoor falls (and relatively active, healthy people at high risk for outdoor falls) (11).

A previous history of falls is also a significant risk factor for further falls (12). Several studies document that the risk of falling increases dramatically as the number of risk factors increases. One study reported the percentage of people falling increased from 27% for those with no or one risk factor, to 78% for those with four or more (13).

Approximately half of hip fractures occur in women whose BMD is above the osteoporotic range (14−16). Several longitudinal studies have shown that the risk of hip fractures is associated with falls risk factors (17). The falls risk factors that, independently of BMD, predict hip fractures include a history of falls, fall to the side, self reported health, self reported physical activity, impaired cognition, slower walking speed, type II diabetes mellitus, Parkinson's disease, poor vision and depth perception, lack of exercise in the last year, frailty and muscle composition (17).

A French prospective study (OFELY) of 672 postmenopausal women followed up for a mean of 5.3 years showed that past falls independently predicted incident osteoporotic fracture (OR 1.76; CI 1.00−3.09) (18). In the Study of Osteoporotic Fractures (SOF) 9516 white women over 65 years were followed up for an average of 4.1 years. In SOF, a fall in the previous year predicted hip fracture (RR 1.6; CI 1.2−2.1 in the age adjusted model and RR 1.4; CI 1.0−2.1 in the multivariate model). Hip fracture risk increased 30% per fall from 0 falls to 5 or more falls (RR 1.30 per fall; CI 1.1−1.5). However, after adjustment for inability to rise from a chair, spending four hours or less on one's feet and poor health, a history of falls or number falls were no longer significantly associated with hip fractures (19). In a further analysis of SOF, among non-osteoporotic women, characteristics which increased fracture risk included falls in the previous year, reduced visual contrast sensitivity and lack of exercise in the previous year (20).

Data from Sweden on 1076 women found that, although previous fractures were good predictors of future fragility fractures in those aged less than 70 years, in later life falling tendency became the important predictor (21). An analysis from the European Prospective Osteoporosis Study showed that low BMD was less predictive than falls for predicting limb fractures in women across European populations (22). The French EPIDOS study found four independent fall-related predictors of hip fracture: slower gait speed, difficulty doing a tandem (heel-to-toe) walk, reduced visual acuity and small calf circumference. The rate of hip fracture among women classified as high risk (top quartile risk) based on both a high fall-risk status and low BMD was 29 per 1000 woman years, compared with 11 per 1000 for women classified as high risk status for low BMD and 5 per 1000 woman-years with low risk for both criteria (23). More recent data from the UK on 3200 women aged 65−84 (COSHIBA Cohort for Skeletal Health in Bristol and Avon) found a history of falls was an independent risk factor of future fracture (OR 1.68; CI 1.46−1.92). Apart from age, there were relatively few other independent risk factors for fracture (the only ones being current bisphosphonate and calcium and vitamin D treatment, suggesting that fracture liaison services in the area were targeting bone protective therapy successfully to those with a fracture history) (24).

In men, analysis from a Danish Cohort (SOMA study) suggests that when compared to men without a history of falls, those who reported one fall were significantly more likely to fracture (HR 1.56; CI 1.06−2.31). A higher prevalence of falls was associated with increased hazard ratios (2−4 falls per year: HR 2.18 CI 1.41−3.37; >4 falls per year: HR 2.46 CI 1.12−5.41) (25).

Frailty and Sarcopenia

The concept of frailty is associated with fracture risk (26). There is a lack of a standardised definition of frailty, though combinations of weight loss, reduced physical activity, walking speed and muscle strength are usually included. One population-based cohort study found that frailty doubled the risk for recurrent falls over a one to two year follow-up, and also led to a three-fold increase in risk of hospitalization compared to non-frail elderly men and women (27). In a 9-year prospective study, frailty increased the risk of falls by 40%. Furthermore, after adjusting for age, BMD, falls and fracture history, BMI and co-morbidity, frailty increased the risk of hip fractures by 40%, non-vertebral fractures by 30% and mortality by 80% (28).

Sarcopenia is another concept that is linked to higher falls risk and hip fracture, as well as lower BMD and decreased physical functioning (26,29). The term "sarcoporosis" (Fig. 1) has also been advocated as the combination of sarcopenia and osteoporosis to identify those with high risk for fracture (30).

It is often argued that both frailty and sarcopenia are reflected in an increased falls risk, and that there may be little gained by using all three parameters when considering fracture prediction. In a group of 984 randomly selected women aged 75 years a recalled fall was the most important predictor of future falls and more time-consuming objective functional tests (gait, balance, muscle strength and visual acuity) were of limited importance for fall prediction by comparison (31).

Other Fracture Risk Prediction Tools

In addition to the FRAX tool, other fracture risk calculators are available online including the Garvan fracture risk and the QFractureScores calculators. The Garvan tool [www.garvan.org.au] is based on data from the Australian Dubbo Osteoporosis epidemiology study of more than 2500 men and women age 60 years or more. It differs from FRAX by including a history of falls (subdivided as 0, 1, 2, >2), and the number of previous fractures (subdivided as 0, 1, 2, >2), but does not include other FRAX included risks such as parental history of hip fracture, secondary osteoporosis, rheumatoid arthritis, corticosteroid use, smoking and alcohol. In comparison to Garvan, FRAX tends to

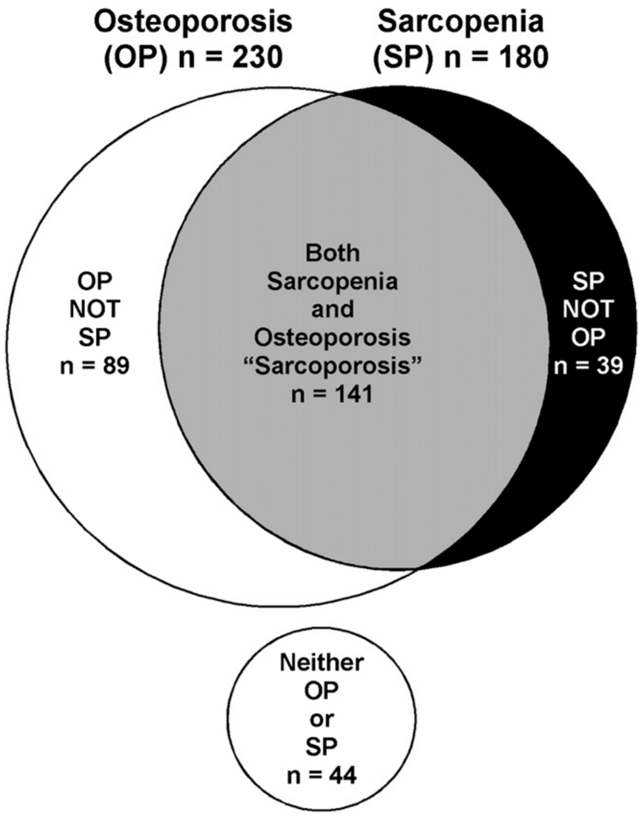

Fig. 1. The Sarcoporosis Concept [Adapted from Di Monaco, et al. *(30)*].

underestimate hip fracture risk in patients with two or more previous fractures and with two or more recent falls. Garvan underestimates fracture risk in those with a parental history of hip fracture and in women with secondary osteoporosis *(17)*. The 10-year fracture risk differences can be quite marked in certain situations. For example, a woman aged 80 years, with a weight of 70 kg and height of 170 cm, the presence of three recent falls and three previous fractures would have a FRAX 10-year hip fracture risk of 11% and Garvan 10 year hip fracture risk of 90%. In contrast, with no other risks, if the same woman had a parental history of hip fracture, her 10-year FRAX hip fracture risk would be 23% compared to a Garvan hip fracture risk of 6.7%. A comparative retrospective validation study between FRAX and Garvan in an Australian population aged 60−90 years showed that in women the 10-year major fracture probability was consistently higher in the fracture than in the non-fracture group: Garvan (0.33 vs. 0.15), FRAX −US (0.30 vs. 0.19), FRAX UK (0.17 vs. 0.10). However in men, only the Garvan discriminated between the fracture and non-fracture groups: Garvan (0.32 vs. 0.14), FRAX-US (0.17 vs. 0.19), FRAX-UK (0.09 vs. 0.12) *(32)*. In a another comparative study of 2012 Polish women aged 55−90 years, ROC AUCs for FRAX and Garvan respectively were 0.833 and 0.879 for any fracture and 0.726 and 0.850 for hip fractures *(33)*. The authors suggested that as Garvan performed better, information on

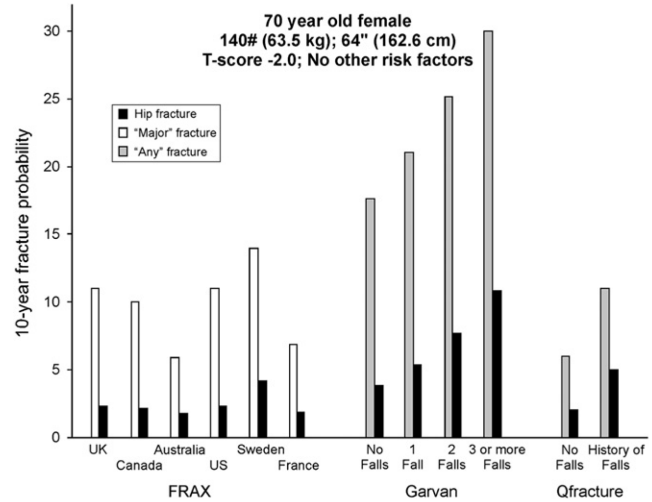

Fig. 2. Comparison of 10-year fracture risk estimates using three fracture risk tools.

number of falls during the last year and multiple fractures ought to be incorporated into the methods of fracture risk prediction. In a study from Holland of 284 patients presenting with a fracture, the 10-year fracture risk was 15% (CI 13−17) higher with Garvan as compared to FRAX. In this cohort, based on UK guidelines (NOGG − National Osteoporosis Guideline Group), treatment was advocated in 74% of patients based on Garvan compared to 23% with FRAX *(34)*.

The QFracture Scores tool is based on a UK prospective open cohort study of routinely collected data from 357 general practices on over a million women and over a million men aged 30−85 years (www.qfracture.org). Like the FRAX tool it takes into account history of smoking, alcohol, corticosteroid use, parental history (of hip fracture or osteoporosis) and several secondary causes of osteoporosis (more comprehensive than FRAX). Unlike FRAX it also includes a history of falls (yes/no only) and excludes previous fracture history and BMD. Using the example of a 170 cm tall 80 year old woman, weighing 70 kg with three previous falls and three fractures (as above), the QFractureScores tool predicts the 10-year hip fracture risk to be 14%. If she had no history of falls the 10-year risk would be 7% *(35)*. The difference in fracture risk estimation from these three fracture risk calculators is demonstrated in Figure 2.

Pharmacotherapy for Fracture Reduction in Fallers

Pivotal randomised controlled trials of anti-osteoporotic therapies including alendronate *(36,37)*, risedronate *(38)*, zoledronate *(39)*, denosumab *(40)* and strontium ranelate (post hoc) *(41)* show that the risk of hip fractures can be reduced, but only in high risk patients (previous fractures and/or low BMD). Risedronate is the only drug investigated to-date where hip fracture was the primary endpoint. Hip fractures were reduced significantly by 30% in the overall group (aged 70 years and over), by 40% in those aged 70−79 with

T-scores <-2.5, and by 60% in those with previous vertebral fracture. In the group over age 80 years, the majority of whom were selected on the basis of falls risk factors without necessarily having proven low BMD, there was a non-statistically significant 20% reduction in hip fractures *(38)*. Similarly, although alendronate reduced hip fractures in patients aged 55−81 years with a prevalent vertebral fracture and with patients with a prevalent vertebral fracture or a femoral neck T-score of <-2.5, it did not reduce hip fractures in patients without documented low BMD or prevalent vertebral fracture *(36,37)*.

However these data do not mean that fall risk should not be used in calculating fracture prediction. The bisphosphonate clodronate has been shown to decrease osteoporotic fracture risk in elderly women *(42)*, and is effective in those identified to be at high risk using the FRAX tool *(43)*. In a further post hoc analysis of this study, fracture reduction was similar in women with or without recent multiple falls or in those with impaired ability in rising from a chair compared to those with no such impairment. This suggests that falls or falls risk may not significantly impact on the anti-fracture efficacy of bisphosphonates *(44)*.

Some authors have suggested that further development will be needed for optimal integration of bone and fall related risks, as well as clustering of fractures and integration of risk factors to validate models in different populations and to validate the ability to select patients who will achieve fracture risk reduction with anti-osteoporotic therapy. One suggestion is that FRAX may be used as a primary model and in patients with recurrent fractures and falls the use of the Garvan model may be of additional value *(45)*.

Further, as adherence to osteoporotic medications is quite poor, even amongst those with a recent diagnosis of fracture, e.g., only 52% were adherent to medication treatment at six-month follow-up *(46)*, the addition of fall related risks might improve the acceptance of osteoporosis treatment and improve understanding of the consequences of severe falls.

Interventions to Prevent Falls

As the majority of non-vertebral fragility fractures are caused by a fall, it is important that all patients with osteoporosis, prior osteoporotic fracture and those deemed to be at high fracture risk are assessed for falls risk and considered, if at high risk, for interventions aimed to reduce falls risk. Falls may go without clinical attention for a number of reasons and the patient may not mention the event to a medical staff as they sustained no significant injury or they may believe that falls are a normal part of ageing. Thus, it is critical that older people are routinely asked about falls (particularly those falls occurring indoors). International guidelines recommend asking older people annually about falls and carrying out a simple assessment of gait/balance that can direct subsequent specialist falls assessment to address modifiable risk factors *(10)*. It may be impossible to completely prevent falls, but it may be possible to reduce the frequency.

Interventions to reduce falls can be classified into three main types: single (one intervention only), multiple (fixed combination of two or more intervention delivered to all participants) and multifactorial (more than one intervention, the combination given depending on an individual assessment of risk factors). A recent Cochrane review has outlined the current evidence for different interventions in preventing falls among older people living in the community *(47)* (a separate Cochrane review is available for those living in long term care facilities). The review summarised 111 randomised studies involving over 55,000 people, although most of the studies excluded patients with cognitive impairment; a major risk factor for falls. The primary outcomes of the studies were either rate of falls (presented as rate ratios; RaR) or number of fallers (risk ratios; RR) or both.

Single Interventions

1. Exercise

Exercise interventions can be grouped into six main components: 1. Gait and/or Balance Training and/or Functional Training; 2. Strength Training; 3. Flexibility; 4. 3-D training (such as Tai Chi or dance); 5. General Physical Activity; 6. Endurance.

Exercise (group) classes containing multiple components (two or more) significantly reduced both rate of falls (RaR 0.78; 95% CI = 0.71−0.86) and risk of falling (RR 0.83; 0.72−0.97). A subgroup analysis showed that for falls rate, this type of intervention was effective in the subgroup selected on the basis of high falls risk on enrolment, and for the unselected subgroup; whereas for the risk of falling the multiple exercise intervention reduced risk significantly only in the high risk selected subgroup.

Home-based exercise including more than one exercise component significantly reduced both fall rates (RaR 0.66; 0.53−0.82) and risk of falling (0.77; 0.61−0.97). Tai-Chi (which actually contains a combination of both strength and balance training) also significantly reduced the rate (RaR 0.63; 0.52−0.78) and risk (RR 0.65; 0.51−0.82) of falling. Interventions focusing on only one type of exercise did not reduce falls with the exception of the gait/ balance/functional training group alone, which reduced the rate of falling (RaR 0.73; 0.54−0.98) but not the risk. In general the results of the Cochrane review on exercise are consistent with previous findings that high level exercise, and exercise which challenges balance, are effective in reducing falls *(48)*. Pooled data from 719 participants in five trials showed that the risk of fractures was reduced from exercise interventions (RR 0.36; 0.19−0.70), suggesting that interventions designed to reduce falls may also reduce fractures *(47)*.

2. Medication Modification

Medication use is a well-documented risk factor for falls and one of the most modifiable. Medications commonly implicated include neuroleptics, benzodiazepines, antidepressants and anti-hypertensives. The combination effect of multiple medications is also implicated and an older person on more than three medications is at increased risk of falls

(49). Further, poor adherence to medications was found to increase the rate of falls by 50% in one cohort study of elderly men and women (46). Medication review is therefore critical in the assessment of older people who fall. There was a significant reduction in the risk of falls following an education programme for primary care physicians (RR 0.61; 0.41–0.91) (50). In a randomised trial, gradual withdrawal of psychotropic medication was found to reduce the rate of falls (RaR 0.34; 0.16–0.73) compared to a control group, but not the risk of falls (51).

A meta-analysis performed in 2004 suggested that vitamin D (including vitamin D analogues) supplementation significantly reduced the risk of falls by 22% in ambulatory or institutionalised patients (52). The current Cochrane review on falls in the community dwelling population did not find any statistically significant difference in the overall risk or rate of falls with vitamin D supplementation (13 trials). However, a post hoc subgroup analysis showed that the rate of falls was significantly reduced in trials recruiting participants with lower vitamin D levels (RaR 0.57; 0.37–0.89) (47). This suggests that vitamin D intervention may only be effectively reduce falls in those who are vitamin D insufficient or deficient. There is current debate on what is the optimum circulating level of 25-hydroxyvitamin D and what dose of vitamin D is needed to reduce falls and fractures.

Two trials of alfacalcidol found no effect on rate or risk of falls but did show a significant reduction in number of people sustaining a fracture (53). One trial using calcitriol observed a statistically significant reduction in rate of falls and risk of falling (54). However both of these vitamin D compounds significantly increased hypercalcaemia risk.

3. Environmental

Home safety interventions were not found to significantly reduce the rate or number of people falling except for those in those with severe visual impairment (VA 6/24 or worse), where the rate of falls was significantly reduced (RaR 0.59; 0.42–0.82). A subgroup analysis carried out by falls risk at enrolment showed that in the high falls risk group, home safety intervention led to a significant reduction in rate of falling (RaR 0.56; 042–0.76) compared to a no intervention control group, whereas in the low falls risk group there was no significant reduction (47).

4. Improving Vision

Cumming et al evaluated vision assessment and eye examination – expediting ophthalmology treatment and new prescriptions for glasses (55). This showed a statistically significant increase in the rate and number of fallers with a non-significant increase in fractures. The authors believe this result may be due to the fact that many participants in this trial required major changes to their prescriptions and therefore during this period of adjustment the risk of falls may increase. However, another study showed that expediting first cataract surgery did significantly reduce the rate of falls when compared to waiting list controls (RaR 0.66, 0.45–0.95) (56).

5. Other Single Interventions

In patients with carotid sinus hypersensitivity, implantation of dual chamber pacemakers led to a significant reduction in fall rates (RaR 0.42; 0.23–0.75) compared to a control group (57).

Multiple Interventions

In an eight arm factorial design study investigating various combination of three interventions (exercise, home hazard management and vision improvement plus placebo), the risk of falling was significantly reduced in all three combinations which included exercise – exercise + home safety (RR 0.76; 0.60–0.97), exercise + vision improvement (RR 0.73; 0.59–0.91) and all three (RR 0.67; 0.51–0.88) (58). The single interventions alone, or the home safety + vision improvement, showed no significant effect in this study.

A combination of education, home safety and exercise intervention found a significant reduction in the rate of falls (RaR 0.69; 0.5–0.96) (59). A Thai study showed a significant reduction in falling risk with a combination of an educational programme and free access to a geriatric clinic (60).

Multifactorial Interventions

In a meta-analysis of 15 trials, multifactorial interventions did show a significant reduction in the rate of falls ((RaR 0.75; 0.65–0.86) although there was substantial heterogeneity between individual studies in the pooled data (47). No significant reduction in risk of falls or fractures was seen. The effectiveness of multifactorial interventions may be influenced by healthcare systems. For example three studies in Holland failed to reproduce the successful multi-factorial intervention in a population of UK fallers presenting to the emergency departments who were randomised to a home environmental assessment and a comprehensive geriatric assessment at a geriatric day hospital (47,61). Possible reasons for the differences include discrepancies in time between assessment of risk factor and the interventions received and differences in provision of care in the existing general population which would affect rate of falls in the control groups.

A recent study from the USA has shown that dissemination of evidence about fall prevention, coupled with interventions to change clinical practice, may reduce fall related injuries in older people (62). Furthermore, a Swedish cost-effectiveness analysis of a community based elderly safety promotion programme aimed at preventing falls suggests that it may be as cost-effective as osteoporosis pharmaceuticals in the prevention of hip fractures (63).

Options for Incorporating Falls History in FRAX

The FRAX-Falls Clinical Task Force Sub-Committee discussed the following options for incorporating knowledge of falls risk into the FRAX algorithm:

1. Option 1

Adding the number of falls in the previous year as a separate risk factor to the FRAX algorithm. This would be the ideal solution and the Falls Sub-Committee is of the view that in the longer term the FRAX algorithm should incorporate a falls history into calculating the 10-year fracture risk. Nevertheless the Sub-Committee acknowledges the difficulties faced in proceeding along these lines at the present time.

Falls history was not incorporated into the FRAX algorithms for several reasons. Firstly, among the FRAX developers, there was some doubt that the characterization of risk on this basis would identify a group amenable to therapeutic intervention. The concern arose mainly from the risedronate hip trial (see above) *(38)*. However as the clodronate study showed, treatment works as well in fallers compared to non-fallers. This sub-committee is of the view that there are also other factors included in FRAX model, such as age and parental history of hip fracture, that are not amenable to bone-directed interventions and therefore it is not logical to exclude falls on this basis. Furthermore, as outlined above, there is now robust evidence that interventions (single and multiple) are available that can reduce falls.

Secondly, a falls history was documented in only a minority of cohorts when the FRAX algorithm was developed. Of the 12 original cohorts, only three (25%) had information on falls. There was therefore not the breadth of data compared to the other risk variables. This limited the ability to seek interactions between falls and the other risk variables.

Third, the construct of the question varied between cohorts as shown in the Table below which summarizes the data available to 1997 when the dataset leading to the FRAX algorithm was established. The cohorts in the table below are anonymised, since the FRAX undertook not to publish cohort specific data. Importantly, the prevalence of falls varied markedly, more by question construct than by age.

	A Have you fallen in the past week?		A* Have you fallen in the past month?		B Have you fallen in the last 6 months?		C Have you fallen in the last year?	
Age	Number of patients	% of yes	Number of patients	% of yes	Number of patients	% of yes	Number of patients	% of yes
20−29	175	2.3	175	9.1				
30−39	500	3.2	500	5.4				
40−49	995	2.2	995	7.7				
50−59	1954	2.3	1954	6.7				
60−69	2801	1.9	2801	5.7				
70−79	2278	2.1	2278	7.0	2776	22.5	6292	31.1
80−89	667	2.9	667	7.5	2984	25.3	768	33.2
90−99	51	2.0	51	13.7	135	31.1	2	100.0
100−109	2	0.0	2	0.0	1	0.0		

	D More than 1 fall in the last month?		E Falls last 12 months		F Falls from last visit	
Age	Number of patients	% of yes	Number of patients	% of yes	Number of patients	% of yes
50−59					6	0
60−69			1900	24.1	1092	24.2
70−79	2710	3.1	2706	27.6	778	34.6
80−89	2023	4.1	522	31.0	265	41.1
90−99	94	8.5	15	46.7	22	45.5
100−109	1	0.0	3	66.7		

A* Two questions in the same cohort.

Fourth, falls were associated with a significant increase in fracture in some, but not all, cohorts used in the development of FRAX. There was therefore heterogeneity in the outcome, possibly related to the heterogeneity of the construct of the question. Of 10 falls questions for 16 outcomes recorded (an outcome may be variously hip fracture, all fractures, etc) a significant increase in risk was observed in 4, but with a point estimate above unity in 14 of 16. From the original FRAX cohorts data, the view that falls consistently increase fracture risk worldwide is plausible, though the level of evidence derived from these datasets was not considered to be of the highest quality of study evidence.

In the longer term it is essential that there be standardization of the falls data collected, e.g., number of falls in the previous year, so that some of the issues outlined above can be resolved. Until additional datasets are available which allow incorporation of falls into the FRAX algorithm in a robust way, the FRAX team should examine ways of incorporating information from other studies such as SOF or other large observational studies. For example the SOF data suggests that each extra fall (up to 5 or more) in the previous year increases the 10-year hip fracture risk by 30% (see above). The subgroup acknowledges that several assumptions would need to be accepted if this approach is adopted.

2. Option 2

In the absence of incorporating falls history into the FRAX algorithm, the other option, in the shorter term would be to make the FRAX user aware of the current limitations of FRAX (i.e., lack of falls as a risk in this case, which is likely to underestimate 10 year risks in patients with falls, especially recurrent falls). Accompanying advice could include a statements like, ‘‘Data from the Study of Osteoporotic Fractures suggest that in comparison to individuals without a fall in the previous year, a history of each fall (up to 5 falls or more) in the previous year increases the 10 year hip fracture risk by approximately 30 % in women.’’ This would allow the FRAX user, if they wished, to adjust the 10-year fracture risk estimates.

3. Option 3

The falls subgroup considered whether other parameters such as sarcopenia, frailty and functional status could also be incorporated in FRAX in trying to further improve 10 year fracture risks. Although there are studies suggesting this approach may have some utility, the view of the subcommittee was that a falls history incorporated these parameters. For a busy clinician, asking a falls history is straight forward and not time-consuming, whereas assessing sarcopenia, frailty or functional status are problematic, suffer from lack of universally accepted definitions and assessment tools, are time-consuming, and therefore will not be practical. The subcommittee’s view is therefore that for the present, these other parameters should not be added to the risk factors in FRAX per se, although in the future as further evidence is produced on their usefulness in improving fracture prediction, they may be reconsidered.

4. Option 4

The falls sub-committee views fall prevention as an essential management aim in the prevention of future fractures. Pharmacotherapy cannot prevent all fractures and at best can only reduce hip fracture risk by approximately 40% and non-vertebral fractures by around 25%. Further fracture reduction therefore will require measures to reduce falls risk in addition to treatment directed at the bone. The evidence that falls can be prevented is now considerable (as above). The guidance given to clinicians in FRAX therefore should include statements about the importance of falls prevention. Options include developing a care pathway for falls assessment and management, or linking to an existing guideline such as the combined American Geriatrics Society and British Geriatrics Society Guidelines on Falls *(10)*.

Additional Question for Future Research

It is suggested that future studies evaluate whether combining standard bone directed osteoporosis treatment strategies, (e.g., bisphosphonates) with strategies to assess and reduce falls risk will have an additive effect on fracture risk reduction. Though it is intuitive that combination therapy directed at bone and falls risk would further reduce fractures; demonstration of this in properly designed clinical trials and subsequently identifying optimal combination approaches is necessary. An additional area of research could focus on injurious falls. Could implementation of injurious falls into the FRAX model enhance identification of those at risk for fragility fracture?

In Summary

The FRAX tool is an established method, used worldwide, to estimate 10-year fracture risk that can aid discussion with patients and help in decisions regarding treatment for osteoporosis and in fracture prevention. A number of limitations have recently been identified including the lack of incorporation of a falls history. There is some evidence that, in comparison to some other fracture prediction tools, FRAX may underestimate fracture risk in individuals with a history of falls. This FRAX-Falls subcommittee has reviewed the evidence and has made some suggestions on how falls can be incorporated into FRAX. In the longer term the ideal solution would be add falls as a risk factor into the FRAX algorithm, when future standardized datasets which include falls history at baseline become available. In the shorter term guidance should be given to the FRAX users on how to take into account a falls history when interpreting the calculated FRAX 10 year fracture risks.

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References

1. Allolio B. 1999 Risk factors for hip fracture not related to bone mass and their therapeutic implications. Osteoporos Int 9(Suppl 2):S9−S16.
2. Masud T, Morris RO. 2001 Epidemiology of falls. Age Ageing 30(Suppl 4):3−7.
3. Austin N, Devine A, Dick I, et al. 2007 Fear of falling in older women: a longitudinal study of incidence, persistence, and predictors. J Am Geriatr Soc 55(10):1598−1603.
4. Deshpande N, Metter EJ, Lauretani F, et al. 2008 Activity restriction induced by fear of falling and objective and subjective

measures of physical function: a prospective cohort study. J Am Geriatr Soc 56(4):615−620.
5. Salkeld G, Cameron ID, Cumming RG, et al. 2000 Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ 320(7231):341−346.
6. Berry SD, Miller RR. 2008 Falls: epidemiology, pathophysiology, and relationship to fracture. Current Osteoporosis Reports 6(4):149−154.
7. Tinetti ME, Kumar C. 2010 The patient who falls: ‘‘It’s always a trade-off’’. JAMA 303(3):258−266.
8. Woolcott JC, Richardson KJ, Wiens MO, et al. 2009 Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 169(21):1952−1960.
9. Leveille SG, Jones RN, Kiely DK, et al. 2009 Chronic musculoskeletal pain and the occurrence of falls in an older population. JAMA 302(20):2214−2221.
10. American Geriatrics Society BGS. AGS/BGS Clinical Practice Guideline: Prevention of falls in older persons. 2010 (December 12, 2010, http://www.americangeriatrics.org/education/prevention_of_falls.shtml).
11. Kelsey JL, Berry SD, Procter-Gray E, et al. 2010 Indoor and outdoor falls in older adults are different: the maintenance of balance, independent living, intellect, and Zest in the Elderly of Boston Study. J Am Geriatr Soc 58(11):2135−2141.
12. Nevitt MC, Cummings SR, Kidd S, Black D. 1989 Risk factors for recurrent nonsyncopal falls. A prospective study. JAMA 261(18):2663−2668.
13. Tinetti ME, Ginter SF. 1988 Identifying mobility dysfunctions in elderly patients. Standard neuromuscular examination or direct assessment? JAMA 259(8):1190−1193.
14. Schott AM, Cormier C, Hans D, et al. 1998 How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. Osteoporos Int 8(3): 247−254.
15. Black DM, Steinbuch M, Palermo L, et al. 2001 An assessment tool for predicting fracture risk in postmenopausal women. Osteoporos Int 12(7):519−528.
16. Lyles KW, Colon-Emeric C, Magaziner J, et al. 2007 Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357:1799−1809.
17. Geusens P, Van Geel T, van den Bergh J. 2010 Can hip fracture prediction in women be estimated beyond bone mineral density measurement alone. Therapeutic Advances in Musculoskeletal Disease 2:63−67.
18. Albrand G, Munoz F, Sornay-Rendu E, et al. 2003 Independent predictors of all osteoporosis-related fractures in healthy postmenopausal women: The OFELY study. SO - Bone 32(1): 78−85.
19. Cummings SR, Nevitt MC, Browner WS, et al. 1995 Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 332(12): 767−773.
20. Wainwright SA, Marshall LM, Ensrud KE, et al. 2005 Hip fracture in women without osteoporosis. J Clin Endocrinol Metab 90(5):2787−2793.
21. Gardsell P, Johnell O, Nilsson BE, Nilsson JA. 1989 The predictive value of fracture, disease, and falling tendency for fragility fractures in women. Calcif Tissue Int 45(6):327−330.
22. Kaptoge S, Benevolenskaya LI, Bhalla AK, et al. 2005 Low BMD is less predictive than reported falls for future limb fractures in women across Europe: results from the European Prospective Osteoporosis Study. Bone 36(3):387−398.
23. Dargent-Molina P, Favier F, Grandjean H, et al. 1996 Fall-related factors and risk of hip fracture: the EPIDOS prospective study. [Erratum appears in Lancet 1996 Aug 10;348(9024):416]. Lancet 348(9021):145−149.
24. Clark EM, Cuming M, Gould VC, et al. 2010 Risk factors for fractures over aged 50 in a population-based cohort of older women from the UK. JBMR.
25. Frost M, Abrahamsen B, Masud T, Brixen K. 2010 Risk factors for fracture in elderly men. A population-based prospective study.
26. Rolland Y, Abellan van Kan G, Benetos A, et al. 2008 Frailty, osteoporosis and hip fracture: causes, consequences and therapeutic perspectives. Journal of Nutrition, Health & Aging 12(5):335−346.
27. Kiely DK, Cupples LA, Lipsitz LA. 2009 Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. J Am Geriatr Soc 57(9):1532−1539.
28. Lang TF, Cauley JA, Tylavsky F, et al. 2010 Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: The health, aging, and body composition study. J Bone Miner Res 25.
29. Robbins JA, Schott AM, Garnero P, et al. 2005 Risk factors for hip fracture in women with high BMD: EPIDOS study. Osteoporos Int 16(2):149−154.
30. Di Monaco M, Vallero F, Di Monaco R, Tappero R. 2011 Prevalence of sarcopenia and its association with osteoporosis in 313 older women following a hip fracture. Arch Gerontol Geriatr 52(1):71−74.
31. Gerdhem P, Ringsberg KA, Akesson K, Obrant KJ. 2005 Clinical history and biologic age predicted falls better than objective functional tests. J Clin Epidemiol 58(3):226−232.
32. Sandhu SK, Nguyen ND, Center JR, et al. 2010 Prognosis of fracture: evaluation of predictive accuracy of the FRAX algorithm and Garvan nomogram. Osteoporos Int 21: 863−871.
33. Pluskiewicz W, Adamczyk P, Franek E, et al. 2010 Ten-year probability of osteoporotic fracture in 2012 Polish women assessed by FRAX and nomogram by Nguyen, et al. - Conformity between methods and their clinical utility. Bone 46: 1661−1667.
34. Van Geel T, Huntjens K, Bours S, et al. 2010 Comparison of FRAX and Garvan case finding algorithms in patients presenting with a fracture. Bone 47:S188.
35. Hippisley-Cox J, Coupland C. 2009 Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation of validation of QFractureScores. BMJ 339: b4229.
36. Black DM, Cummings SR, Karpf DB, et al. 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 348(9041):1535−1541.
37. Cummings SR, Black DM, Thompson DE, et al. 1998 Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial. JAMA 280:2077−2082.
38. McClung MR, Geusens P, Miller PD, et al. 2001 Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med 344:333−340.
39. Black DM, Delmas PD, Eastell R, et al. 2007 Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 356:1809−1822.
40. Cummings SR, San Martin J, McClung MR, et al. 2009 Denosumab for prevention of fractures in postmenopausal women with osteoporosis. [Erratum appears in N Engl J Med. 2009 Nov 5;361(19):1914]. N Engl J Med 361(8): 756−765.

41. Reginster JY, Seeman E, De Vernejoul MC, et al. 2005 Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 90(5): 2816−2822.
42. McCloskey EV, Beneton M, Charlesworth D, et al. 2007 Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. J Bone Miner Res 22(1):135−141.
43. McCloskey EV, Johansson H, Oden A, et al. 2009 Ten-year fracture probability identifies women who will benefit from clodronate therapy−additional results from a double-blind, placebo-controlled randomised study. Osteoporos Int 20(5): 811−817.
44. Kayan K, Johansson H, Oden A, et al. 2009 Can fall risk be incorporated into fracture risk assessment algorithms: a pilot study of responsiveness to clodronate. Osteoporos Int 20(12): 2055−2061.
45. van den Bergh JP, van Geel TA, Lems WF, Geusens PP. 2010 Assessment of individual fracture risk: FRAX and beyond. Current Osteoporosis Reports 8(3):131−137.
46. Berry SD, Quach L, Procter-Gray E, et al. 2010 Poor adherence to medications may be associated with falls. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 65(5): 553−558.
47. Gillespie LD, Robertson MC, Gillespie WJ, et al. 2009 Interventions for preventing falls in older people living in the community. Cochrane Database of Systematic Reviews (2): CD007146.
48. Sherrington C, Whitney JC, Lord SR, et al. 2008 Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc 56(12):2234−2243.
49. Leipzig RM, Cumming RG, Tinetti ME. 1999 Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. J Am Geriatr Soc 47(1):40−50.
50. Pit SW, Byles JE, Henry DA, et al. 2007 A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Aust 187(1): 23−30.
51. Campbell AJ, Robertson MC, Gardner MM, et al. 1999 Psychotropic medication withdrawal and a home-based exercise program to prevent falls: A randomized, controlled trial. J Am Geriatr Soc 47:850−853.
52. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. 2004 Effect of vitamin D on falls: A meta-analysis. JAMA 291: 1999−2006.
53. Dukas L, Bischoff HA, Lindpaintner LS, et al. 2004 Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc 52(2): 230−236.
54. Gallagher JC. 2004 The effects of calcitriol on falls and fractures and physical performance tests. J Steroid Biochem Mol Biol 89−90(1−5):497−501.
55. Cumming RG, Ivers R, Clemson L, et al. 2007 Improving vision to prevent falls in frail older people: a randomized trial. J Am Geriatr Soc 55(2):175−181.
56. Harwood RH, Foss AJ, Osborn F, et al. 2005 Falls and health status in elderly women following first eye cataract surgery: a randomised controlled trial. Br J Ophthalmol 89(1): 53−59.
57. Kenny RA, Richardson DA, Steen N, et al. 2001 Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). J Am Coll Cardiol 38(5): 1491−1496.
58. Day L, Fildes B, Gordon I, et al. 2002 Randomised factorial trial of falls prevention among older people living in their own homes. BMJ 325(7356):128.
59. Clemson L, Cumming RG, Kendig H, et al. 2004 The effectiveness of a community-based program for reducing the incidence of falls in the elderly: a randomized trial. J Am Geriatr Soc 52(9):1487−1494.
60. Assantachai P, Praditsuwan R, Chatthanawaree W, et al. 2002 Strategy to prevent falls in the Thai elderly: A controlled study integrated health research program for the Thai elderly. J Med Assoc Thai 85:215−222.
61. Close J, Ellis M, Hooper R, et al. 1999 Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. Lancet 353:93−97.
62. Tinetti ME, Baker DI, King M, et al. 2008 Effect of dissemination of evidence in reducing injuries from falls. N Engl J Med 359(3):252−261.
63. Johansson PM, Sadigh S, Tillgren PE, Rehnberg C. 2008 Non-Pharmaceutical prevention of hip fractures - a cost-effectiveness analysis of a community based elderly safety promotion programme in Sweden. Cost Effectiveness and Resource Allocation 6:11.

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