

Therapeutics Initiative

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Screening to reduce fragility fractures: new trials, still ineffective

Case vignette: Two of your patients recently suffered fractures. One fell while walking, and spent 10 days in hospital recovering from a hip fracture. The other awakened with severe back pain and was found by X-ray to have a new vertebral compression fracture. You wonder if you should invite all your elderly patients to screen for risk factors, and whether this could spare some from a similar fate.

Fragility fractures occur from forces that would not break normal bones. They cause significant morbidity that can limit independence, and are associated with premature death.¹ Therapeutics Letters 83 and 84 presented our systematic review (SR) findings from randomized controlled trials (RCTs) of **oral bisphosphonates** for primary and secondary fracture prevention (benefits and harms).²⁻³ Since our 2011 SR, no new trials of **oral bisphosphonates** for primary prevention have been published. We still conclude that in **primary prevention**, alendronate and risedronate (the 2 oral drugs typically prescribed in BC) do not reduce clinically important fractures. In future we will address evidence about fragility fracture prevention with IV zoledronic acid or SQ denosumab.

This Letter summarizes outcomes of intensive screening programs intended to prevent fractures in older adults. To be effective, a screening program must:⁴

- Reliably identify which healthy people are at high risk of a future condition;
- Facilitate early and effective treatment for people who can benefit; and
- Avoid treatment of people unlikely to benefit.

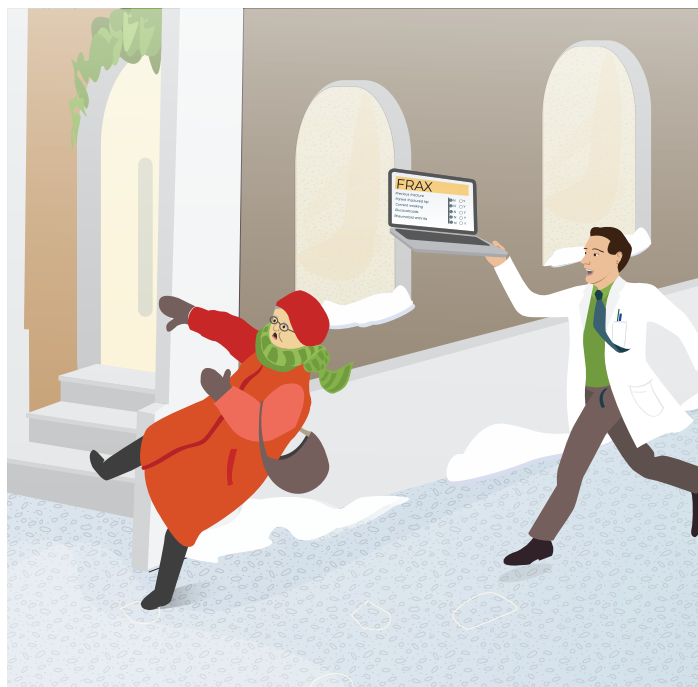
By these criteria, we conclude that risk screening programs for fragility fracture prevention are ineffective.

Screening based on BMD was unsatisfactory

In the 1990s, an international fracture prevention strategy was predicated on the assumptions that low bone mineral density (BMD) predicts clinical fractures, and that treatment with bisphosphonates would prevent them.⁵ It soon became clear that in women with hip fracture, BMD measurements (dual-energy absorptiometry/DXA) overlap greatly with age-matched controls. Screening with BMD inevitably ensures a high proportion of false positives and substantial overdiagnosis.^{6,7} Under recognition was also a problem. About 80% of post-menopausal women who experience fractures are not "osteoporotic", as defined by BMD.⁸

Screening using risk scores

The Fracture Risk Assessment Tool (FRAX®), launched in 2008, uses demographic, health-related and lifestyle risk factors to calculate a



10-year probability of osteoporotic fracture.⁹ It shares the problems of screening with BMD, although it better predicts hip fractures. For example, a Canadian cohort study identified "high risk" FRAX scores (calculated retrospectively) amongst 1,399 people (18% men) as of the dates immediately before their fragility fractures.¹⁰ A "high risk" FRAX designation applied retrospectively to:

- < 43% of people who experienced any fragility fracture;
- < 50% of people who suffered a major fracture;
- < 76% of people who experienced a hip fracture.

Like BMD testing, using FRAX to screen patients expands the definition of a "disease." When employed in guideline-based treatment algorithms like that advocated by the US National Osteoporosis Foundation (NOF), **FRAX scoring directs almost 3/4 of US women over age 65 towards drug treatment.**¹¹

Three large community-based RCTs assessed risk scoring for primary prevention of fragility fractures in 57,744 women enrolled between 2008-2014.¹²⁻¹⁴ (Table) They compared population-based screening and treatment programs with "usual care" that did not mandate use of screening tools, but allowed drug treatments. No individual RCT found a statistically significant reduction in total osteoporotic fractures or major osteoporotic fractures. One RCT identified a 0.9% absolute reduction in hip fractures amongst older women, of whom 22% had prior fragility fracture (NNT 111 over a mean of 4.8 years).¹³

These 3 studies applied screening tools (FRAX +/- BMD) to large populations that included 11-44% of women with prior fragility fractures (2° prevention). The most recent study pre-screened women for 9 clinical risk factors to **identify higher risk patients before randomization.**¹⁴ This Dutch RCT found no significant fracture reductions, even after including only such higher-risk patients (in whom screening as precursor to treatment would be most likely to show benefit).



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Study	Population	Screening Method/Treatment	Outcomes	Fracture Outcomes
ROSE 2018 ¹² Denmark Enrolment 2010-2011 F/U: 5 y (median)	34,229 women Age 65-80 (median: 71) 10.6% 2° prevention	Mailed invitation to complete FRAX (+ BMD if FRAX predicted $\geq 15\%$ risk of major osteoporotic fracture over 10 y) 54% of invitees completed FRAX. High risk informed of results; treatment recommendations to FP. Patients offered bisphosphonates (oral or some IV) or other drugs per Danish guidelines.	Mortality: NR by group SAE: NR QoL: NR Function: NR	Adjusted Sub Hazard Ratio SHR (95% CI) Hip: 1.002 (0.89-1.130) Major: 0.986 (0.922-1.055) OP: NR All: 1.004 (0.946-1.064)
SCOOP 2018 ¹³ England Enrolment 2008-2009 F/U: 4.8 y (mean)	12,483 women Age 70-85 (mean: 75) 22% 2° prevention	FRAX (+ BMD for 'high risk' based on FRAX-generated 10-y hip fracture risk) High risk advised to contact FP "to discuss treatment options"	Mortality: ND SAE: NR QoL: No diff Function: NR	Hazard Ratio HR (95% CI) Hip: 0.72 (0.59-0.89) Major: NR OP: 0.94 (0.85-1.03) All: 0.94 (0.86-1.03)
SOS 2019 ¹⁴ Netherlands Enrolment 2010-2014 F/U: 3.7 y (mean)	11,032 women Age 65-90 (mean: 75) pre-screened & enrolled if >1 risk factor for fracture 44% 2° prevention	FRAX, BMD, VFA (Vertebral Fracture Assessment), falls assessment, blood tests to exclude 2° osteoporosis For high-risk patients, personalized treatment recommendations to FP: alendronate or risedronate + Ca/VitD, notification of high fall risk + additional diagnostics or referral to 2° care.	Mortality: ND SAE: NR QoL: NR Function: NR	Adjusted Hazard Ratio HR (95% CI) Hip: 0.91 (0.71-1.15) Major: 0.91 (0.80-1.04) OP: 0.91 (0.81-1.03) All: 0.97 (0.87-1.08)

F/U: follow-up; FP: family physician; ND: no difference; NR: not reported; SAE: total Serious Adverse Events; QoL: Quality of Life (by validated scales); Function: measure of function/disability by validated scale/tool; **Sub Hazard Ratio** = a competing risk analysis that allows continued accounting for participants who experience outcomes that preclude or alter the chance to experience main study outcome(s); **Hip**: hip fracture; **Major**: "major osteoporotic fracture," usually defined as fracture of the hip, vertebra, wrist, humerus; **OP**: "osteoporotic fracture," usually defined as all fractures except for skull/face, hand/ finger, and foot/toe; **All**: all fractures. A 2018 U.S. Preventive Services Task Force report on screening did not identify 2 of these 3 RCTs.¹⁵

In 2019, the same Dutch authors **meta-analyzed the 3 screening trials**.¹⁶ This analysis excluded 15,624 people (46%) randomized in the largest RCT. It reports no difference in total mortality, or total fractures, but small reductions of "osteoporotic hip fractures," "major osteoporotic fractures," and "all osteoporotic fractures." Due to the multiple differences in the approaches to screening and treatment, we think it more appropriate to consider the RCTs individually, as shown in the **Table**.

Age, falls and some drugs predict fractures

In Swedish women, age-related decrease in BMD could account for a 3.8-fold increase in fracture incidence from age 55 to 85. Over the same 30-year interval, their annual probability of fracture increases 44-fold. Thus age has an 11-fold greater impact on fracture risk than low BMD.¹⁷

A history of falls (independent of other variables) predicts a higher incidence of fragility fractures in women and men than FRAX or BMD would anticipate.¹⁸ **But are interventions to prevent falls effective, and does fall prevention also prevent fractures? Answers remain uncertain.**

Cochrane and U.S. Preventive Services Task Force SRs (RCTs to 2018) concur that exercise and "multifactorial interventions" seem to reduce falls, yet they may not reduce the number of people experiencing injuries, fractures or death.¹⁹⁻²¹ **Exercise alone reduces both the number of people falling and injuries**,¹⁹ and supervised exercise programs are most effective.²² When possible, it is common sense to avoid, reduce, or stop medicines that increase the chance of falls (e.g. sedatives, antihypertensives, hypoglycemics).²³

Common sense to avoid falls: caution in icy/snowy or dark conditions, crossing streets or moving while using a mobile phone, reducing obstacles at home.

Age-specific hip fracture incidence is falling – independent of treatment

Population aging predicts substantial increases in the total number of people experiencing fragility fractures. **But in the U.S. the risk of hip fracture for an individual has been decreasing for decades.** Framingham Heart Study data show a decline beginning after 1980 – at least 10 years before BMD measurements, and 15 years before bisphosphonates were first prescribed. From 1995 through 2010, the 67% reduction in *per capita* hip fracture incidence far exceeds a "best case" estimate of 4.8% attributable to bisphosphonate use. Much of the decline appears attributable to less smoking and heavy alcohol use.²⁴ Similarly, between 1989-1991 and 2009-2011 women in Olmstead County, Minnesota experienced a 25% decline in hip fractures and 26% decline in distal forearm fractures.²⁵ A Swedish case-control study of post-menopausal women also found increased hip fracture risk in current smokers, age-adjusted odds ratio 1.66 (95%CI 1.41-1.95). **But risk decreased after smoking cessation.**²⁶

Conclusions

- As screening tools, BMD and FRAX do not reliably predict who will experience fragility fractures. Age, a history of falls, and use of certain drugs predict risk much better.
- Large RCTs demonstrate that using population-based screening (FRAX +/- BMD) to identify and treat "high risk" patients is not an effective strategy to reduce fragility fractures in post-menopausal women.
- Interventions to prevent falls are desirable, but effects on fracture prevention uncertain. Exercise, smoking cessation, and avoiding excessive alcohol or drugs that increase falls seem most likely to reduce dangerous or disabling fractures.

For the complete list of references go to: www.ti.ubc.ca/FRX

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