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ORIGINAL ARTICLE

Targeted vertebral fracture assessment for optimizing fracture prevention in Canada

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Abstract

Summary Vertebral fracture assessment (VFA) provides incremental information in identifying women and men aged 70 years and older qualifying for anti-osteoporosis treatment compared with FRAX® major osteoporotic fracture (MOF) probability computed with bone mineral density (BMD).

Purpose This analysis was performed to inform appropriate use of VFA testing as part of Osteoporosis Canada's Guidelines Update, assuming vertebral fracture is an indication for pharmacotherapy in women and men.

Methods Women and men aged 70 years and older without previous high-risk fracture (i.e., hip, spine, or multiple fractures) were identified in a BMD registry for the province of Manitoba, Canada. MOF probability with BMD was computed using the Canadian FRAX® tool. VFA was performed in those with a minimum BMD *T*-score of −1.5 or lower.

Results The study population consisted of 7289 women (mean age 76.7 ± 5.6 years) and 1323 men (77.9 ± 5.8 years). More women than men qualified for VFA testing (48.7% vs 25.4%, respectively, $p < 0.001$). Among those undergoing VFA, a vertebral fracture was more commonly detected among men than women (22.9% vs 13.3%, $p < 0.001$), and vertebral fracture prevalence increased with lower BMD *T*-score (both *p* trend <0.001). The number needed to screen with VFA to detect a vertebral fracture was 8 for women and 4 for men. MOF probability was substantially lower in men than in women, and fewer men than women (3.3% vs 20.2%, $p < 0.001$) met a treatment threshold of MOF 20% or greater. In those with MOF probability <20%, VFA identified an incremental 5.4% of men and 3.4% of women for treatment based upon vertebral fracture.

Conclusions The number needed to screen to identify a previously unappreciated vertebral fracture is low and further improves with lower BMD *T*-score. VFA identified more men as qualifying for treatment than MOF probability. In women, treatment qualification was predominantly from MOF probability.

Keywords Osteoporosis · Fracture · Clinical practice guidelines · Dual-energy X-ray absorptiometry · Vertebral fracture assessment

Introduction

Osteoporosis Canada published clinical practice guidelines in 2010 for the assessment and treatment of individuals with osteoporosis [1, 2]. Those guidelines represented a significant departure from earlier recommendations based on the principle that a 10-year fracture risk assessment offered a better strategy for targeting therapy towards high-risk individuals than bone mineral density (BMD) alone (based upon a simple *T*-score definition) [3]. Importantly, BMD alone was not an indication for treatment initiation in the absence of high fracture risk.

The 2010 guidelines included two primary pathways to therapy: prior high-risk fracture (defined as low-trauma fractures of the hip, spine, or multiple fracture episodes at other

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sites excluding the head/neck, hand/feet, and ankle) or high fracture probability as assessed with the Canadian fracture risk assessment (FRAX®) tool (major osteoporotic fracture (MOF) computed with bone mineral density (BMD) over 20%). To facilitate case finding among individuals designated as moderate risk (10–20%), the 2010 guidelines stated "Lateral thoracolumbar radiography (T4–L4) or vertebral fracture assessment (VFA) may aid in decision-making by identifying vertebral fractures."

Osteoporosis Canada is in the process of updating its guidelines. To address the overarching key question "What is the best strategy to identify those at high fracture risk for pharmacotherapy in order to prevent the most fractures?", we conducted extensive simulation analyses which demonstrated that the criterion of MOF with BMD probability ≥20% was an appropriate intervention threshold in the absence of a prior high-risk facture as defined above [4]. We demonstrated that FRAX without BMD offers an effective strategy to identify individuals meeting the intervention threshold and aligned with using an age cutoff of 70 years in the absence of additional clinical risk factors [5].

We next considered the role of targeted VFA with the key question "Should women (men) without known vertebral fractures receive vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays (versus no spine imaging) to find those with vertebral fractures for whom anti-fracture therapy may be given?" The current analysis was undertaken to directly explore the incremental value of targeted VFA in individuals aged 70 years or older versus the FRAX 10-year probability MOF with BMD ≥20% to identify women and men qualifying for pharmacotherapy using a large BMD and VFA registry for the province of Manitoba, Canada. Since 2010, this registry has routinely performed VFA in individuals aged 70 years or older with a minimum BMD *T*-score of ≤−1.5.

Methods

Study population

In the Canadian Province of Manitoba (population 1.3 million in 2017), health services are provided to virtually all residents through a public healthcare system. Dual-energy X-ray absorptiometry (DXA)-based BMD testing is managed as an integrated clinical program; the criteria for testing have been published and include screening at age 65 years for all women and for men and younger women in the presence of additional risk factors [6]. The program maintains a database of all DXA results which can be linked with other provincial population-based computerized health databases through an anonymous personal identifier. The DXA database has completeness and accuracy in excess of 99% [7].

The study population included all women and men aged 70 years and older registered with Manitoba Health and undergoing baseline DXA testing from 2010 (when VFA testing was introduced) to 2018. We excluded individuals with high fracture risk as defined above as they already qualify for treatment under the national guidelines [1, 2]. We also excluded those without healthcare coverage (non-residents of Manitoba). The study was approved by the Health Research Ethics Board for the University of Manitoba.

Bone mineral density measurements and fracture probability

Hip and lumbar spine DXA scans were performed and analyzed in accordance with manufacturer recommendations. Hip *T*-scores (number of SDs above or below young adult mean BMD) were calculated from NHANES III white female reference values [8]. Lumbar spine *T*-scores were calculated from manufacturer white female reference values. The program's quality assurance is under strict supervision by a medical physicist [6]. Cross-calibrated instruments (Prodigy and iDXA, GE enCORE software version 14, GE/Lunar Healthcare, Madison, WI, USA) with between-scanner differences <0.1 *T*-score were used for this study. These densitometers exhibited a stable long-term performance (coefficient of variation <0.5%). All reporting physicians and supervising technologists are required to maintain DXA certification with the International Society for Clinical Densitometry (ISCD).

The 10-year probability of a MOF with femoral neck BMD was calculated for each individual using the Canadian FRAX tool (FRAX® Desktop Multi-Patient Entry, version 3.7), without taking into consideration the VFA status. The inputs used for generating the FRAX scores have been described thoroughly in a recent publication [9]. The Canadian FRAX tool was calibrated using nationwide hip fracture and mortality data [10–12].

Vertebral fracture assessment

As noted above, individuals aged 70 years or older qualified for VFA if they had a *T*-score of ≤−1.5 (minimum lumbar spine, total hip, or femoral neck). VFA image interpretation was performed by four physicians certified by the ISCD. The same physician performing the VFA image interpretation also reported the accompanying DXA scans for BMD as previously described [9]. The reporting physician assessed for presence of vertebral fracture with the modified algorithm-based qualitative (ABQ) method, using the morphologic criteria of endplate depression or cortical discontinuity and excluding non-fracture causes of vertebral deformity (such as degenerative remodeling, Scheuermann's disease, and Schmorl's nodes) [13–15]. Suspected traumatic and pathologic vertebral fractures are identified and excluded through an intake

questionnaire that asks about previous fracture mechanism and review of spine imaging available in the province-wide Picture Archiving and Communications System (PACS). A random sample of 127 images, half of which were reported to be VFA fracture positive and half VFA negative, showed high inter-rater agreement with two independent expert readers not involved in the original reading, both blinded to the clinical readings (kappa scores 0.86 and 0.78, respectively). VFA images for each individual were recorded as (a) positive for vertebral fracture (one or more vertebral fractures definitely present), (b) negative for vertebral fracture, (c) uncertain for vertebral fracture (usually with a recommendation for additional imaging), or (d) unsatisfactory quality (i.e., most vertebral levels uninterpretable). No additional information was recorded in terms of the level, severity, or number of vertebral fractures or numbers of non-evaluable vertebrae. For the current analysis, we conservatively assumed that only definite vertebral fractures would be considered positive and that uncertain results ($N = 119$) and unsatisfactory scans ($N = 24$) would be considered negative.

Statistical analysis

Baseline characteristics of the study population were calculated and reported according to sex and compared using Student's *t* test or the χ^2 test of independence as appropriate. All analyses were stratified by sex. We estimated the percent of individuals qualifying for pharmacotherapy based upon MOF probability ≥20% or positive VFA, with a particular focus on the incremental value of VFA defined as individuals positive for vertebral fracture with MOF probability <20%. VFA positivity was assessed in relation to *T*-score categories (−1.50 to −1.99, −2.00 to −2.49, and −2.5 or lower), and the Cochran-Armitage test was used to examine for linear trend. Statistical analyses were performed with Statistica (Version 13.0, StatSoft Inc., Tulsa, OK, USA).

Results

The study population characteristics are summarized in Table 1. Men were slightly older than women but on average had higher BMD *T*-scores and were correspondingly less likely to have BMD in the osteoporotic range (all $p < 0.001$). MOF probability was substantially lower in men than in women, and many fewer men than women (3.3% vs 22.2%, $p < 0.001$) met the MOF treatment threshold of ≥20%.

Due to lower mean BMD *T*-score, more women qualified for VFA than men (48.7% vs 25.4%, $p < 0.001$). Among women and men qualifying for VFA, mean age was similar, 77.4 and 77.8 years respectively. The mean lowest BMD *T*-score was higher in men than in women qualifying for VFA, though the difference was reduced compared with all individuals. Once again, MOF probability was significantly greater among women compared with men resulting in a larger percentage of women meeting the MOF treatment threshold (28.9% vs 5.7%, $p < 0.001$). Among individuals undergoing VFA, a vertebral fracture was more commonly detected among men than women (22.9% vs 13.3%, $p < 0.001$).

Table 2 shows the breakdown in individuals qualifying for treatment according to vertebral fracture detected from VFA or MOF probability 20% or greater stratified by minimum BMD *T*-score category (−1.50 to −1.99, −2.00 to −2.49, and

Table 1 Characteristics of the study population stratified by sex

	Women	Men	*p* value
All individuals	$N = 7289$	$N = 1323$	
Age (years)	76.7 ± 5.6	77.9 ± 5.8	<0.001
Minimum *T*-score	−1.9 ± 1.2	−1.2 ± 1.2	<0.001
Osteoporotic *T*-score	2345 (32.2)	294 (22.2)	<0.001
MOF probability with BMD percent	15.0 ± 7.9	8.5 ± 4.5	<0.001
MOF probability with BMD ≥20%	1473 (20.2)	44 (3.3)	<0.001
VFA performed	3551 (48.7)	336 (25.4)	<0.001
VFA-detected vertebral fracture (all individuals)	472 (6.5)	77 (5.8)	0.369
Individuals qualifying for VFA	$N = 3551$	$N = 336$	
Age (years)	77.4 ± 5.7	77.8 ± 5.8	0.177
Minimum *T*-score	−2.6 ± 0.7	−2.3 ± 0.6	<0.001
Osteoporotic *T*-score	1726 (48.6)	166 (49.4)	0.780
MOF probability with BMD percent	17.6 ± 7.9	11.0 ± 5.0	<0.001
MOF probability with BMD ≥20%	1028 (28.9)	19 (5.7)	<0.001
VFA-detected vertebral fracture (all individuals)	472 (13.3)	77 (22.9)	<0.001

Data expressed as mean (SD) or *N* (percent)

MOF major osteoporotic fracture, *BMD* bone mineral density

Table 2 Breakdown in treatment qualification according to vertebral fracture detected from VFA or MOF-BMD probability, stratified by sex and T-score

Criterion for treatment qualification	Sex		*T*-score −1.00 or greater	*T*-score −1.01 to −1.49	*T*-score −1.50 to −1.99	*T*-score −2.00 to −2.49	*T*-score −2.5 or lower	Row total
VFA	Women	No fracture	NA	NA	772	780	1527	3079
		Fracture	NA	NA	53	91	328	472
		Not performed	1697	721	396	264	659	3737
		Total	1697	721	1221	1135	2514	7288
		Treated, vertebral fracture detected	NA	NA	6.4%	10.4%	17.7%	13.3%
		Number needed to screen with VFA to detect vertebral fracture	NA	NA	16	10	6	8
	Men	No fracture	0	0	107	84	68	259
		Fracture	0	0	17	18	42	77
		Not performed	553	169	110	70	85	987
		Total	553	169	234	172	195	1323
		Treated, vertebral fracture detected	NA	NA	13.7%	17.6%	38.2%	22.9%
		Number needed to screen with VFA to detect vertebral fracture	NA	NA	7	6	3	4
MOF-BMD probability	Women	<20%	1672	678	1128	942	1395	5815
		≥20%	25	43	93	193	1119	1473
		Total	1697	721	1221	1135	2514	7288
		Treated, high MOF-BMD probability	1.5%	6.0%	7.6%	17.0%	44.5%	20.2%
	Men	<20%	550[a]	162	227	165	174	1280[a]
		≥20%	<6[a]	7	7	7	21	45[a]
		Total	553	169	234	172	195	1323
		Treated, high MOF-BMD probability	<1%[a]	4.1%	3.0%	4.1%	10.8%	3.3%

VFA vertebral fracture assessment, *MOF-BMD* major osteoporotic fracture probability estimated with bone mineral density (BMD)

[a] Rounded due to small cell size

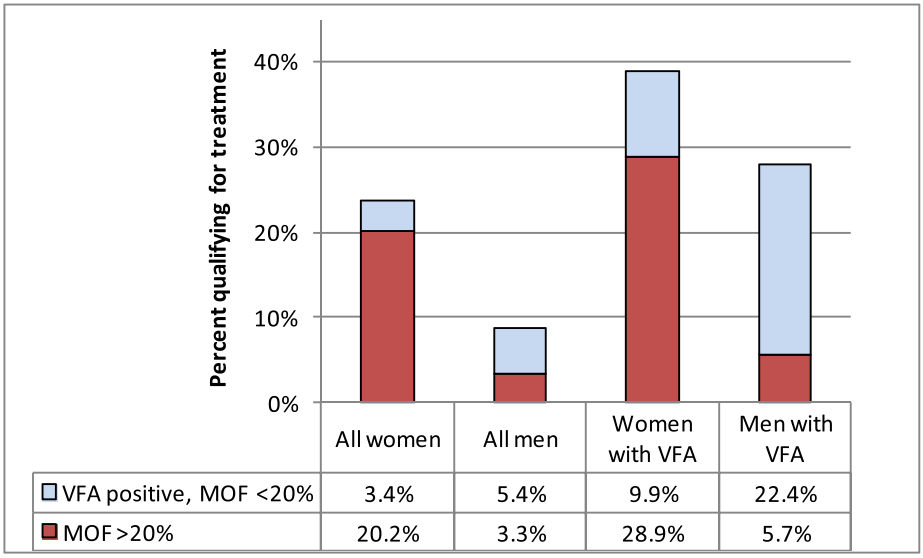
Table 3 Cross-tabulation in treatment qualification according to vertebral fracture detected from VFA or MOF-BMD probability, stratified by sex

Sex	MOF-BMD probability	VFA no fracture	VFA fracture	VFA not done	Row total
All individuals					
Women	<20%	2272 (31.2)	*251 (3.4)*[b]	3293 (45.2)	5816 (79.8)
	≥20%	807 (11.1)	221 (3.0)	445 (6.1)	*1473 (20.2)*[b]
	Total	3079 (42.2)	472 (6.5)	3738 (51.3)	7289 (100)
Men	<20%	246 (18.6)	*71 (5.4)*[b]	962 (72.7)	1279 (96.7)
	≥20%	13 (1.0)	6 (0.5)	25 (1.9)	*44 (3.3)*[b]
	Total	259 (19.6)	77 (5.8)	987 (74.6)	1323 (100)
Excluding aromatase inhibitor users, glucocorticoid users, and any prior fracture					
Women	<20%	1755 (35)	*194 (3.9)*	2464 (49.1)	4413 (87.9)
	≥20%	339 (6.8)	87 (1.7)	179 (3.6)	*605 (12.1)*
	Total	2094 (41.7)	2094 (41.7)	281 (5.6)	2643 (52.7)
Men	<20%	163 (18.6)	*46 (5.3)*[b]	649 (74.3)	858 (98.2)
	≥20%	7 (0.8)	S (<1)[a]	8 (0.9)	*15 (1.8)*[ab]
	Total	170 (19.5)	50 (5)[a]	657 (75.2)	875 (100)[a]

VFA vertebral fracture assessment, *MOF-BMD* major osteoporotic fracture probability estimated with bone mineral density (BMD)

[a] Rounded due to small cell size. [b] Two non-overlapping pathways to treatment qualification: vertebral fracture with MOF-BMD <20%, MOF-BMD ≥20%

a All subjects.



b Excluding aromatase inhibitor users, glucocorticoid users, any prior fracture.

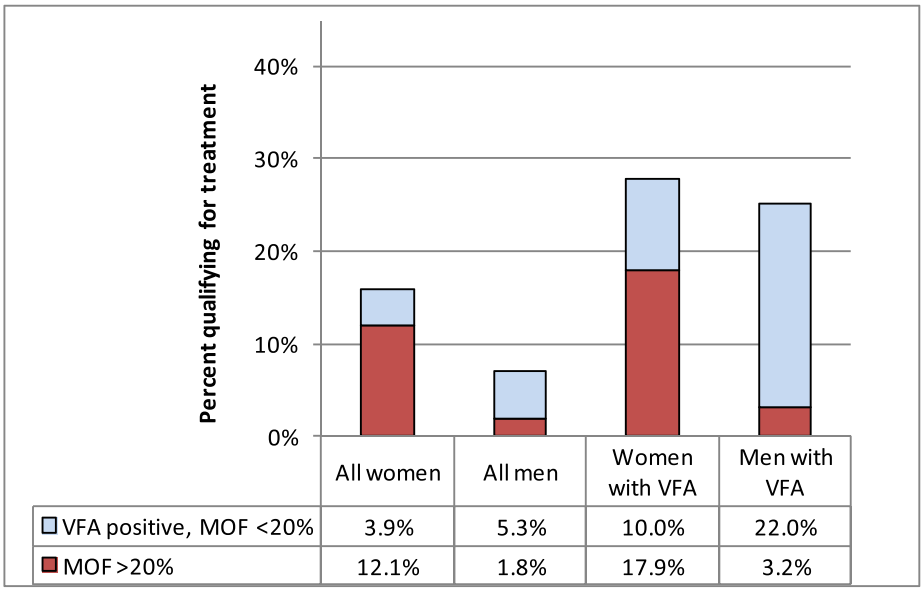


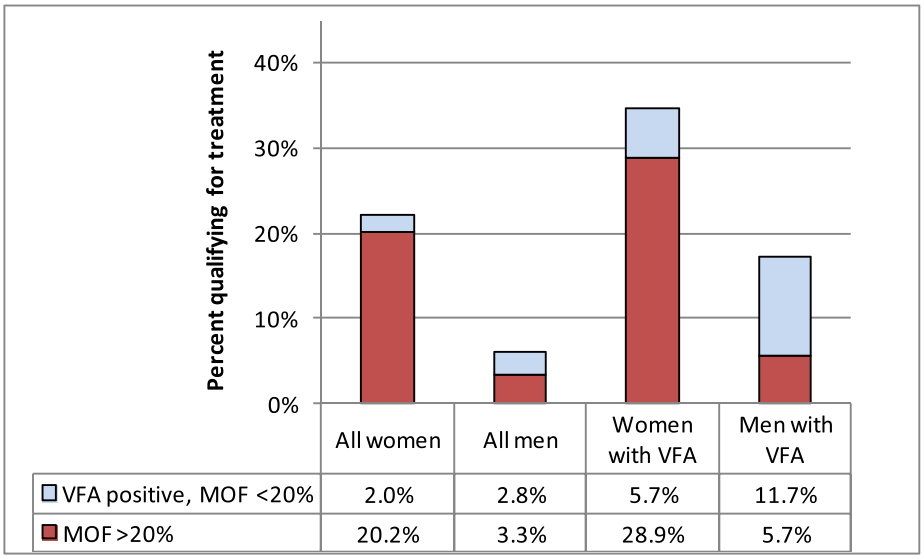
Fig. 1 Percent qualifying for osteoporosis treatment based upon vertebral fracture detected by VFA (all individuals) or MOF probability with BMD ≥20%, stratified by sex. **a** All subjects. **b** Excluding aromatase inhibitor users, glucocorticoid users, and any prior fracture

−2.5 or lower). The percentage of women found to have vertebral fracture increased with lower BMD *T*-score: 6.4%, 10.4%, and 17.7% (p trend <0.001). A similar pattern was seen for men: 13.7%, 17.6%, and 38.2%, respectively (p trend <0.001). The number needed to screen with VFA to detect a vertebral fracture was 8 for all women combined (range 6 to 16) and 4 for all men combined (range 3 to 7). Using a BMD *T*-score cutoff of −2.5 for VFA testing would have identified 69.5% of women and 54.5% of men with vertebral fractures detected by VFA while avoiding 47.8% and 67.3% of the VFAs performed, respectively. A cut off of −2.0 for VFA testing would have identified 88.8% and 77.9% of the vertebral fractures detected by VFA while avoiding 23.2% and 36.9% of the VFAs performed, respectively. Qualification for treatment based upon MOF probability also increased with lower BMD *T*-score in women and men (all p trend <0.001). Qualification for treatment was very unlikely with the BMD *T*-score in the normal range (1.5% in women and <1% in men) and increased to 44.5% in women and 10.8% in men with a BMD *T*-score in the osteoporotic range.

Results were stratified to look at the incremental treatment qualification from VFA versus MOF probability (Table 3). Vertebral fracture was identified on VFA in 3.4% of women with MOF-BMD less than 20% (9.9% for women undergoing

VFA). Vertebral fracture was identified in 5.4% of men with MOF probability less than 20% (22.4% of men undergoing VFA). Results were generally similar after excluding individuals with other selected risk factors (aromatase inhibitor users, glucocorticoid users, and any prior non-trauma fracture). Figure 1 shows that among women, treatment qualification was predominantly from MOF-BMD, including women undergoing VFA and excluding those with additional risk factors. However, VFA identified more men qualifying for treatment than MOF probability (similar among men qualifying for VFA and after exclusion of those with selected risk factors). When VFA was restricted to individuals with BMD *T*-score −2.5 or lower, findings were generally similar except that fewer men qualified for treatment based upon VFA compared with MOF probability (2.8% vs 3.3%), though VFA again identified more men for treatment in those undergoing VFA after excluding those with additional risk factors (Fig. 2). When both sources of treatment qualification were considered (vertebral fracture identified on VFA or MOF-BMD probability 20% or greater) among all individuals (Table 3), VFA was responsible for 14.6% of the treatment qualification in women (19.6% of women undergoing VFA). In contrast, among men, 61.7% qualified for treatment based upon VFA (78.9% of those undergoing VFA).

a All subjects, T-score -2.5 or lower.



b Excluding aromatase inhibitor users, glucocorticoid users, any prior fracture.

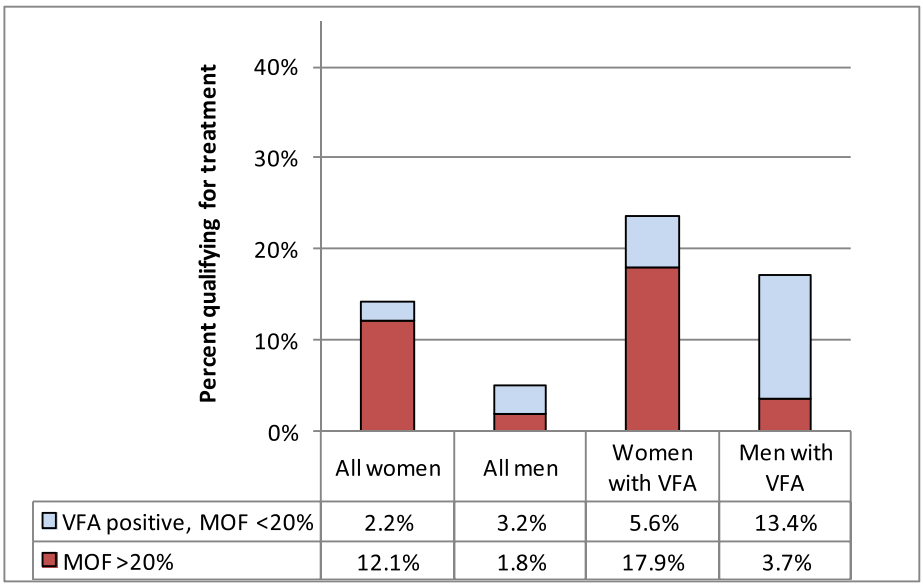


Fig. 2 Percent qualifying for osteoporosis treatment based upon vertebral fracture detected by VFA (individuals with *T*-score −2.5 or lower) or MOF probability with BMD ≥20%, stratified by sex. **a** All subjects, *T*-score −2.5 or lower. **b** Excluding aromatase inhibitor users, glucocorticoid users, and any prior fracture

Discussion

We found that VFA provides incremental information in identifying women and men aged 70 years and older qualifying for anti-osteoporosis treatment compared with MOF probability alone. There was generally a good yield for VFA in terms of prevalence of vertebral fracture and the number needed to screen, which increased with lower BMD *T*-score and the expense of a decrease in sensitivity. The greatest yield from VFA in terms of fraction of individuals with vertebral fracture detected was seen with a BMD *T*-score in the osteoporotic range, and this translated into the lowest number needed to screen (6 in women and 3 in men). The value of VFA was overall greater among men than women, offsetting the lower treatment qualification from MOF probability in men.

Equity is an important consideration in guidelines development under the GRADE procedure, the process used for the Canadian guideline update [16–19]. Lower MOF probability scores are generated by FRAX in men than women despite identical inputs, reflecting the importance of competing mortality in the calculation. VFA was more likely to affect treatment qualification in men than in women. Sex disparity was greatly reduced when both pathways to treatment qualification were considered (vertebral fracture from VFA and/or MOF probability ≥20%).

Our findings are important to see in the context of other vertebral imaging guidelines. The US National Osteoporosis Foundation (NOF) recommends vertebral imaging for all women aged 70 and older and all men aged 80 and older if BMD *T*-score at the spine, total hip, or femoral neck is ≤−1.0, with additional criteria for younger individuals [20]. We were unable to evaluate the utility of VFA for individuals with BMD *T*-score above −1.5 since such individuals do not qualify for VFA testing in Manitoba. The ISCD and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) proposed VFA testing criteria which are similar to those from NOF [21–24]. The UK National Osteoporosis Guidelines Group (NOGG) suggests that VFA be considered in postmenopausal women and older men if there is a history of ≥4 cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, and BMD *T*-score ≤−2.5 and in individuals with a history of non-vertebral fracture after the age of 50 years [25]. The Dutch guidelines recommend a systematic evaluation of vertebral fractures in those with a recent non-vertebral fracture and a BMD *T*-score between −1.0 and −2.5 [26]. The choice of BMD *T*-score criterion for VFA testing needs to consider trade-offs between sensitivity for detecting vertebral fracture versus savings in time and costs. Schousboe et al. [27] has previously shown that VFA with selective confirmatory radiography is cost-effective for postmenopausal women aged 60 to 80 years at various combinations of age and BMD *T*-score.

Limitations to the current analysis are acknowledged. In this clinical registry, individuals selected for BMD testing may be at higher risk than the general population. This is particularly the case for men referred for BMD testing in Manitoba and likely accounts for the unexpectedly higher prevalence of vertebral fracture detection compared with women. It is unclear whether this would affect extrapolation to the general elderly population. Although efforts were made to identify and exclude traumatic vertebral fractures as noted earlier, trauma could still be contributing to the higher prevalence of vertebral fractures among men. We acknowledge that there is controversy about the radiologic diagnosis of vertebral fracture, particularly in men due to a high prevalence of non-fracture vertebral deformities [28–30]. Therefore, we conservatively used criteria for vertebral fracture diagnosis that are based upon features which have been most strongly associated with incident non-vertebral fracture outcomes [15] and which we have shown to strongly predict those same outcomes in our cohort [9]. We did not study the utility of VFA in individuals younger than age 70 years, who might benefit from VFA based upon other clinical criteria including height loss (reported or measured) or prior glucocorticoid use. Finally, our findings were specifically tailored to the Canadian setting and may not be applicable to other FRAX tools and/or intervention cutoffs or where intervention strategies include hip fracture probability and/or BMD *T*-score.

In summary, our findings help to clarify the situation where vertebral fracture detection from VFA is most likely to affect treatment decision making and may help to refine VFA testing criteria for Canada. The 2010 Osteoporosis Canada guidelines recommended vertebral imaging from VFA or X-ray in individuals with moderate risk (MOF probability 10–20%) [1, 2]. A simpler approach to selecting individuals for VFA based upon age and BMD *T*-score could facilitate a more widespread use of targeted VFA for vertebral fracture detection.

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Authors' contributions Authors' roles: conception, design, analysis, drafting the article (WDL), interpretation of data (all authors); critically revising the article for important intellectual content (all authors); final approval of the version to be published (all authors); and agreement to be accountable for all aspects of the work (all authors). WDL had full access to all the data in the study and takes the responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

The results and conclusions are those of the authors, and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred. This article has been reviewed and approved by the members of the Manitoba Bone Density Program Committee.

Conflicts of interest William Leslie and Lisa Lix have no conflicts of interest. Neil Binkley has nothing to declare for the context of this paper but has received research support (paid to institution) from Radius and GE Healthcare and consultant/advisory board fees from Amgen.

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