Appendix 10: GRADE Evidence to Decision Framework

Question: Should we screen adults ≥40 years to prevent fragility fractures?

POPULATION:	Adults ≥40 years old (community dwelling)	**BACKGROUND:** Fragility fractures are broken bones that result from a minor fall or normal activity that usually should not cause a fracture in healthy adults (1). These fractures occur due to weakened bone structure often referred to as osteoporosis (2). The most common sites of fragility fractures are the hip, spine and wrist (2). As people age, old bone cells may not be replaced by new cells as quickly resulting in brittle or fragile bones (3). This gradual loss of bone density and strength increases the risk of fracture. Risk factors for fragility fracture include low bone density, female sex[1], older age, lower body weight, prior fragility fracture, parental history of hip fracture, a history of falls, chronic use of certain medications (e.g., glucocorticoids), smoking, higher levels of alcohol use, and living with diabetes and/or rheumatoid arthritis (4–8). Post-menopausal females are at a greater risk due to additional bone loss associated with menopause (9). The annual rate of hip fractures among Canadians was 168 per 100,000 (age 65-79 years) and 1,045 per 100,000 (age 80+ years) in 2016 (10). The annual rate for any type of fracture was 843 and 2,642 per 100,000 (ages 65-79 and 80+ years respectively) (10). In the 2010/2011 fiscal year, among Canadians ≥50 years, there were 131,443 fragility fractures associated with 64,884 acute care admissions and 983,074 hospitalized days (11). The cost of fragility fractures was estimated at $4.6 billion
INTERVENTION:	**KQ1**: Screening to prevent fragility fractures (BMD-first or risk assessment-first screening strategies) **KQ2**: Validated fracture risk assessment tool (with or without BMD) **KQ3**: Alendronate, risedronate, zoledronic acid, denosumab, any bisphosphonate **KQ4:** N/A	
COMPARISON:	**KQ1a**: No screening; KQ1b: other screening strategies **KQ2**: N/A **KQ3**: No treatment or placebo **KQ4**: N/A	
MAIN OUTCOMES:	**Critical:** **KQ1/3:** Benefits: Reductions in hip fractures, all clinical fragility fractures and fracture-related	

[1] The terms “female” and “male” are referring to sex (i.e., biological attributes, particularly the reproductive or sexual anatomy at birth), unless otherwise indicated.

Appendix 10, as supplied by the authors. Appendix to: Thériault G, Limburg H, Klarenbach S, et al. Recommendations on screening for primary prevention of fragility fractures. *CMAJ* 2023. doi: 10.1503/cmaj.221219.

	mortality. Increased functionality and disability, quality of life or wellbeing. Harms: Serious adverse events (including all serious cardiovascular events; serious cardiac rhythm disturbances (e.g. atrial fibrillation or ventricular arrhythmia); serious gastrointestinal (GI) events (excluding cancers); GI cancer; atypical femoral fractures; osteonecrosis of the jaw; rebound fractures. **Important:** **KQ1/3:** Benefits: Reduction in all-cause mortality Harms: Overdiagnosis (KQ1 only), discontinuation due to adverse events, non-serious adverse events (including any adverse events or adverse (drug) reactions; any non-serious adverse events) **KQ2:** Calibration for 5 and 10 year fracture risk of hip and all clinical fractures **KQ4:** Acceptability of screening and/or treatment, willingness or intention to screen or initiate treatment, magnitude of benefit to make screening and/or treatment acceptable	including acute, rehabilitation and long-term care as well as prescription drug cost, wage loss and home care (11). The World Health Organization (WHO) suggests that BMD T-score of less than -2.5 (2.5 or more standard deviations below the reference mean) is a significant risk factor for fragility fractures and refers to it as osteoporosis (12). The prevalence of low bone density (<-2.5) in Canada among aged 65-79 years was 17.9 % and 23.6% for those aged 80+ years (10). Among Canadians over 40 years of age, females were four times more likely to report having osteoporosis than males (13). A common screening tool for the risk of fragility fracture is the measurement of bone mineral density (BMD) at the femoral neck (hip) using DXA (dual energy X-ray absorptiometry) (4). The absolute fracture risk can be estimated (with or without BMD) using a risk assessment tool (e.g. FRAX, QFracture (UK Fracture risk assessment), Garvan (Australian Fracture risk assessment), CAROC (Canadian risk assessment)) which provides a percentage risk or risk category for hip or osteoporotic fracture in the next 10 years (14). The goal of screening is to allow clinicians to identify those at risk for fragility fractures and provide appropriate treatment. In 2015, 7.1% of Canadians reported receiving a BMD test (10). Pharmacological treatment to prevent fragility fractures includes first-line therapy for post-menopausal females of bisphosphates (alendronate, risedronate or zoledronic acid) or denosumab (15). Recommended first line therapy for males includes alendronate, risedronate and zoledronic acid (4). Adequate intake of calcium and
SETTING:	Primary care in Canada	

PERSPECTIVE:	Population	vitamin D along with exercise, smoking cessation and fall prevention strategies are also recommended following a diagnosis of elevated fracture risk (2,4). The consequences of fragility fractures include significant morbidity due to disability and chronic pain as well as hospitalization and long-term care admission (4,16,17). Quality of life can be significantly impacted following a fragility fracture, with lower health utility index scores and considerable deficits on mobility and self-care indicators (4,16–18). Fragility fractures also result in a higher mortality particularly among elderly patients with significant comorbidities (19). In fact, patients with bone density have approximately 1.5 times the mortality risk for each standard deviation (T-score) decrease in BMD (20). Since the risk of low bone density increases with age, comorbidities such as diabetes and hypertension are common and increase the risk of mortality following a fracture. However, hip fracture is associated with a 10-45% mortality rate within the first year and an estimated 26-28% of deaths among vertebral fracture patients can be attributed to the fracture alone (20). The increased mortality rates associated with low bone density is also affected by the location of the fragility fracture (e.g. hip), patient sex and ethnicity (20). Screening to prevent fragility fractures may itself cause unintended consequences associated with the screening test, diagnosis and/or treatment. Overdiagnosis can also occur with the identification of high risk in individuals that if not screened would never have known they were at risk and would never experience a fracture.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○No ○Probably no ○Probably yes **X** Yes ○Varies ○Don't know	Screening for the risk of fragility fractures was judged by the Task Force to be a priority problem. This is based on incidence of fragility fractures in Canada and the associated consequences (reduced quality of life, increased morbidity and mortality). There may also be variations in practice and uncertain patient values and preferences. **Number of people affected (burden)** • The annual rate of hip fractures among Canadians was 168 per 100,000 (age 65-79 years) and 1,045 per 100,000 (age 80+ years) in 2016 (10). • The annual rate for any type of fracture was 843 and 2,642 per 100,000 (ages 65-79 and 80+ years respectively) (10). • The cost of fragility fractures (fiscal year 2010/2011) was estimated at $4.6 billion including acute, rehabilitation and long-term care as well as prescription drug cost, wage loss and home care (11). **Potential Consequences** • Fewer than 50 % of Canadians who experience a hip fracture will have a full recovery, and many are permanently disabled (21). • Approximately 25 % of patients will need a nursing home or assisted living care for a year or more after a hip fracture (21). • Mortality was significantly increased among Canadian females 1 year post hip fracture (HR=3.0, 95%CI 1.0-8.7) and post vertebral fracture (HR=3.7, 95%CI 1.1-12.8) (19). **Uncertainty for practice** • Among females aged 50–64 years, 23.1% of females were identified for BMD testing under the USPSTF guidelines and 52.3% under the Osteoporosis Canada guidelines. Osteoporosis Canada also recommends screening males >=65 years with BMD however (4), the USPSTF found insufficient evidence to make a recommendation for males (6). • Canadian and American guidelines recommend a BMD-first screening approach for females over age 65 while European guidelines recommend a risk assessment-first screening (FRAX or QFracture followed by BMD) (4,6,7,22).	

		There is also considerable uncertainty in patient values and preferences (particularly around acceptability of treatment), as there are no comprehensive reviews available.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial **X Small (Females ≥65 years)** ○Moderate ○Large ○Varies **X Don't know (Males ≥40 years and females 40-64 years)**	**KQ1a: What are the benefits of screening compared with no screening to prevent fragility fractures and related morbidity and mortality in primary care for adults ≥ 40 years?** **SUMMARY: JUDGEMENT OF BENEFITS** **All Eligible: (Offer-to-screen in general population, females 45-54 years)** **Screening may not reduce all-cause mortality. The evidence for hip and clinical fragility fractures is very uncertain.** **All Eligible (Offer-to-screen to females ≥65 years in the general population)** **Screening may not reduce hip fractures, clinical fragility fractures, or all-cause mortality.** **"Selected Populations" (Offer-to-screen to females ≥65 years willing to independently complete a mailed fracture risk questionnaire, females ≥65 years)** **Screening probably reduces hip fractures and probably slightly reduces clinical fragility fractures. It probably does not reduce all-cause mortality and there may be little-to-no difference in quality of life.** **"Selected Populations" (Offer-to-screen to males ≥65 years willing to complete a cardiovascular health study and attend a follow-up visit): The evidence for hip fragility fractures is very uncertain.** **No studies reported on fracture-related mortality, functionality or disability.** **No studies reported on men 40-64 years.**	**Definitions:** **Fracture risk assessment tools (e.g. FRAX, CAROC)** - Provide a 10-year probability of fracture based on clinical risk factors with or without bone mineral density. **Bone mineral densitometry (BMD)** - Also called "dual-energy x-ray absorptiometry" (DXA or DEXA) - Includes BMD of either the hip and/or spine - Provides a T-score of a patient's BMD (standard deviation from the average healthy adult BMD) **BMD-first screening:** All patients go directly to BMD without initial fracture risk assessment (may also include post

EVIDENCE TABLES

Table 1.1: Hip fractures

- The evidence about all eligible / offer-to-screen populations (females 45-54 years) is very uncertain.
- **Screening may not reduce hip fracture in *all eligible / offer-to-screen populations* (females 68-80 years).**
- The evidence about acceptors of screening (females 45-54 years) is very uncertain.
- **Screening probably reduces hip fractures in *selected populations*[2] (females ≥65 years; 4.0-6.2 fewer per 1000, NNS=250). (3-5 year follow-up)**
- The evidence for offer-to-screen in *selected*[3] *populations* (males≥65 years) is very uncertain.

Study approach	Population Studies[4]; Sample size	Anticipated absolute effects			Relative HR (95% CI)	Certainty	Judgement
		Assumed population risk*	Risk with screening (95% CI)	Absolute difference (95% CI)			
All eligible / offer-to-screen	Females 45-54 y; 1 RCT (23) (APOSS); 2,797 Follow-up: 9 years	Control event rate (study data)			0.95 (0.19 to 4.71)	Very Low[a-d]	Very uncertain
		2 per 1000	1.9 per 1000 (0.4 to 9.42)	0.1 fewer in 1000 (1.6 fewer to 7.4 more)			
		General population risk*					
		8 per 1000	7.6 per 1000 (1.5 to 37.7)	0.4 fewer in 1000 (6.5			

BMD fracture risk assessment (e.g. FRAX+BMD) to calculate treatment eligibility)

Risk assessment-first screening
- Fracture risk assessment (e.g. FRAX), followed by BMD only if necessary (e.g. based on threshold or shared decision making). Fracture risk should then be re-estimated using FRAX + BMD to calculate treatment eligibility.

All clinical fragility fractures (includes sub-outcomes of
(a) Fractures reported in study as "clinical fractures"
(b) Add up non-vertebral + clinical vertebral
(c) (*Note: Only used for KQ3a and*

[2] Females ≥65 years willing to independently complete a mailed fracture risk questionnaire
[3] Males ≥65 years who were study participants in the CHS - Cardiovascular Health Study (i.e. willing to complete the CHS and attend a follow-up visit)
[4] See Appendix for details on individual studies

					fewer to 29.7 more)			
	Females 68-80 y; 1 RCT (ROSE) (24); 34,229 Follow-up: 5 years	Control event rate (study data)			0.99 (0.88 to 1.11)	Low[a-c]	**May not reduce**
		35 per 1000	34.7 per 1000 (30.8 to 38.9)	0.3 fewer in 1000 (4.2 fewer to 3.9 more)			
		General population risk*					
		20 per 1000	19.8 per 1000 (17.6 to 22.2)	0.2 fewer in 1000 (2.4 fewer to 2.2 more)			
Acceptors of screening	Females 45-54 y; 1 RCT (23) (APOSS); 2,604 Follow-up: 9 years	Control event rate (study data)			0.37 (0.04 to 3.52)	Very Low[a-d]	Very uncertain
		2 per 1000	0.7 per 1000 (0.1 to 7.0)	1.3 fewer per 1000 (1.9 fewer to 5.0 more)			
		General population risk*					
		8 per 1000	3.0 per 1000 (0.3 to 28.2)	5.0 fewer per 1000 (7.7 fewer to 20.2 more)			
Offer-to-screen in <u>selected population</u>[2]	Females ≥65 y; 3 RCTs + 1 CCT (SALT, SCOOP,	Control event rate (study data)			0.80 (0.71 to 0.91)	Moderate to High[c]	**Probably reduces**
		31 per 1000	24.8 per 1000 (22.0 to 28.2)	**6.2 fewer per 1000 (9.0 fewer to 2.8 fewer)**			
		General population risk*					

sensitivity analysis showed no effect on the conclusions). All fractures (reported in study as "all fractures" or add up non-vertebral + any vertebral (clinical, morphologic or unstated)

Major osteoporotic fracture (MOF)
In the literature the term MOF (major osteoporotic fracture) is often defined as a fracture of the hip, spine (clinical), wrist or humerus.

The 10 years fracture risk for females in Canada: 6.7% 35-44 years; 8.3% 45-54 years; 13.9% 55-64 years; 31.8% 75-84 years (Canadian multicenter osteoporosis study 2015) (27)

A similar systematic review of SCOOP, ROSE and SALT (98)

	ROSE + Kern) (24–27); 43,736 Follow-up: 3-5 years	20 per 1000	16.0 per 1000 (14.2 to 18.2)	**4.0 fewer per 1000 (5.8 fewer to 1.8 fewer)**				
Offer-to-screen in <u>selected population</u>[3]	Males ≥65 y; 1 CCT (Kern) (27); 1,380 Follow-up: 4.9 years	Control event rate (study data)			0.68 (0.32 to 1.43)	Very Low to Low[a-d]	Very uncertain	
		30 per 1000	20.4 per 1000 (9.6 to 42.9)	9.6 fewer per 1000 (20.4 fewer to 12.9 more)				
		General population risk*						
		16 per 1000	10.9 per 1000 (5.1 to 22.9)	5.1 fewer per 1000 (10.9 fewer to 6.9 more)				

CCT: clinical controlled trial; CI: confidence interval; RCT: randomized controlled trial; y: years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision
*The effects without screening for the general risk population are estimated from Prior et al., 2015, based on 10 year follow-up (28)

Table 1.2: Clinical fragility fractures

- The evidence for all eligible / offer-to-screen (females 45-54 years) is very uncertain.
- **Screening <u>may not reduce</u> clinical fragility fractures in *all eligible / offer-to-screen*** (females 68-80 years).
- **Screening <u>probably slightly reduces</u> clinical fragility fractures in *selected populations*[5] (females ≥65 years; 5.9-11.8 fewer per 1000, NNS=85).** (3-5 year follow-up)

found "a significant reduction of (major) osteoporotic fractures and hip fractures after screening using fracture risk assessment and bone densitometry compared with usual care." Reduction of osteoporotic fractures (HR = 0.95, 95% confidence interval (CI) = 0.89–1.00), Major osteoporotic fractures (HR = 0.91; 95%CI = 0.84–0.98), and hip fractures (HR = 0.80; 95%CI = 0.71–0.91), Numbers needed to screen to prevent one fracture were 247 and 272 for osteoporotic fractures and hip fractures, respectively (corresponding to 113 and 124 performed bone densitometry

[5] Females ≥65 years willing to independently complete a mailed fracture risk questionnaire

- The evidence for acceptors of screening (females 45-54 years) is very uncertain.

Study approach	Population Studies; Sample size	Anticipated absolute effects			Relative HR (95% CI)	Certainty	Judgement
		Assumed population risk*	Risk with screening (95% CI)	Absolute difference (95% CI)			
All eligible / offer-to-screen	Females 45-54 y; 1 RCT (APOSS) (23); 2,797 Follow-up: 9 years	Control event rate (study data)			1.01 (0.68 to 1.50)	Very Low[a-d]	Very uncertain
		34 per 1,000	34.3 per 1000 (23.1 to 51.0)	0.3 more per 1,000 (10.9 fewer to 17.0 more)			
		General population risk*					
		67 per 1,000	67.7 per 1000 (45.6 to 100.5)	0.7 more per 1,000 (21.4 fewer to 33.5 more)			
	Females 68-80 y; 1 RCT (ROSE) (24); 34,229 Follow-up: 5 years	Control event rate (study data)			0.99 (0.92 to 1.06)	Low[a-c]	**May not reduce**
		100 per 1,000	99.0 per 1000 (92.0 to 106.0)	1.0 fewer per 1,000 (8.0 fewer to 6.0 more)			
		General population risk*					
		168 per 1,000	166.3 per 1,000 (154.6 to 178.1)	1.7 fewer per 1,000 (13.4 fewer to 10.1 more)			

examinations, and 25 and 28 persons being treated).

Acceptors of screening	Females 45-54 y; 1 RCT (APOSS) (23); 2,604 Follow-up: 9 years	Control event rate (study data)			0.73 (0.46 to 1.14)	Very Low[a-d]	Very uncertain	
		34 per 1,000	24.8 per 1,000 (15.6 to 38.8)	9.2 fewer per 1,000 (18.4 fewer to 4.8 more)				
		General population risk*						
		67 per 1,000	48.9 per 1,000 (30.8 to 76.4)	18.1 fewer per 1,000 (36.2 fewer to 9.4 more)				
Offer-to-screen in <u>selected population</u>[5]	Females ≥65 y; 3 RCTs (SALT, SCOOP, ROSE) (24–26); 42,009 Follow-up: 3-5 years	Control event rate (study data)			0.93 (0.87 to 0.99)	Moderate[c]	**<u>Probably slightly reduces</u>**	
		84 per 1000	78.1 per 1000 (73.1 to 83.2)	**5.9 fewer per 1000 (10.9 fewer to 0.8 fewer)**				
		General population risk*						
		168 per 1000	156.2 (146.2 to 166.3)	**11.8 fewer per 1000 (21.8 fewer to 1.7 fewer)**				

CCT: clinical controlled trial; CI: confidence interval; RCT: randomized controlled trial; y: years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision
*The effects without screening for the general risk population are estimated from Prior et al., 2015, based on 10 year follow-up (28)

Table 1.3: All cause-mortality

- The evidence about all eligible / offer-to-screen (females 45-54 years) using the assumed population risk from the study data is very uncertain.
- **Screening <u>may not reduce</u> all-cause mortality in females 45-54 years (*all eligible / offer-to-screen*)** based on the assumed population risk found in the general population
- **Screening <u>probably does not reduce</u> all-cause mortality for *offer-to-screen in selected populations*[6]** (females ≥65 years) (3-5 year follow-up).

Study approach	Population Studies; Sample size	Anticipated absolute effects			Relative HR (95% CI)	Certainty	Judgement
		Assumed population risk*	Risk with screening (95% CI)	Absolute difference (95% CI)			
All eligible / offer-to-screen	Females 45-54 y; 1 RCT (APOSS) (23); 4,800 Follow-up: 9 years	Control event rate (study data)			0.99 (0.72 to 1.35)	Very Low to Low[b,d]	Very uncertain
		33 per 1000	32.7 per 1,000 (23.8 to 44.6)	0.3 fewer per 1,000 (9.2 fewer to 11.6 more)			
		General population risk*				Low to Moderate[b,d]	**<u>May not reduce</u>**
		3 per 1,000	3.0 per 1,000 (2.2 to 4.1)	No difference per 1,000 (0.8 fewer to 1.1 more)			
	Females 68-80 y;	Control event rate			0.97 (0.92-1.03)	Low[b,d]	**<u>May not reduce</u>**
		118 per 1000	114.5 per 1000 (108.6 to 121.5)	3.5 fewer per 1000 (9.4 fewer to 3.5 more)			
		General population risk*					

[6] Females ≥65 years willing to independently complete a mailed fracture risk questionnaire

	1 RCT (ROSE) (24); 34,299 Follow-up: 5 years	57 per 1000	55.3 per 1000 (52.4 to 58.7)	1.7 fewer per 1000 (4.6 fewer to 1.7 more)			
Offer-to-screen in selected population[7]	Females ≥65 y; 2 RCTs + 1 CCT (SALT, SCOOP + Kern) (24–27); 59,740 Follow-up: 3-5 years	Control event rate (study data)			1.00 (0.92 to 1.09)	Moderate[d]	**Probably does not reduce**
		89 per 1000	89.0 per 1000 (81.9 to 94.3)	No difference in 1000 (7.1 fewer to 5.3 more)			
		General population risk*					
		57 per 1000	57.0 per 1000 (52.4 to 62.1)	No difference in 1000 (4.6 fewer to 5.1 more)			

CCT: clinical controlled trial; CI: confidence interval; RCT: randomized controlled trial; y: years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision
*The effects without screening for the general risk population are estimated from Prior et al., 2015, based on 10 year follow-up (28).

Table 1.4: Quality of life or wellbeing

- The evidence about all eligible / offer-to-screen females 45-54 years is very uncertain.
- **Screening may make little to no difference on self-rated health or health related quality of life for *offer-to-screen in selected populations*[7] (females 70-85 y) (3-5 year follow-up).**

[7] Females ≥65 years willing to independently complete a mailed fracture risk questionnaire

Outcome	Study approach	Population Studies; Sample size	Findings	Certainty	Judgement
Wellbeing – self-rated health	All eligible / offer-to-screen	Females 45-54 y; 1 RCT (APOSS) (23); 2,797 Follow-up: 9 years	Good or very good: 69.2% of screened, 68.0% controls Not so good or poor: 12.8% of screened, 14.3% controls	Very Low to Low[a-c]	Very uncertain
	Offer-to-screen in selected population[7]	Females 70-85 y; 1 RCT (SCOOP) (26); 10,661 Follow-up: 3 years	Mental health: MD -0.30, 95% CI -0.86 to 0.26 Physical health: MD 0.30, 95% CI -0.21 to 0.81	Low to Moderate[a-c]	**May be little to no difference**
Wellbeing – health-related quality of life	All eligible / offer-to-screen	Females 45-54 y; 1 RCT (APOSS) (23); 1,217 Follow-up: 2 years	General health perception, mean (SD): 69.7 (21.7) in screened, 69.8 (20.8) in controls	Very Low to Low[a,b]	Very uncertain

	Offer-to-screen in selected population[7]	Females 70-85 y; 1 RCT (SCOOP) (26); 10,661 Follow-up: 3 years	MD 0, 95% CI -0.07 to 0.07	Low to Moderate[a, b]	**May be little to no difference**

CCT: clinical controlled trial; CI: confidence interval; RCT: randomized controlled trial; MD: mean difference; y: years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision

KQ1b: Does the effectiveness of screening to prevent fragility fractures vary by screening program type (i.e., BMD-first vs Risk assessment-first) or risk assessment tool (e.g., FRAX vs CAROC)?

SUMMARY: JUDGEMENT OF BENEFITS (*COMPARING SCREENING STRATEGIES)*

There was no evidence comparing the most common risk assessment tools used in Canada (i.e. FRAX and CAROC).

Evidence for SOF or SCORE tools + BMD (risk assessment-first) vs BMD alone (BMD-first) was very uncertain

EVIDENCE TABLES

Table 2.1: Hip and clinical fragility fracture outcomes by screening program type:

Outcome	Study approach	Population Studies; Sample size	Anticipated absolute effects* (95% CI)			Relative HR (95% CI)	Certainty	Judgement
			Assumed population risk	Risk with BMD-first	Absolute difference			
BMD-first vs. Risk assessment-first (SOF- or SCORE-based tool + BMD) screening								
Hip fractures	All eligible / offer-to-screen	Females 60-80 y;	12 per 1,000	8.4 per 1,000 (5.0 to 14.1)	3.6 fewer per 1,000 (7.0 fewer to 2.1 more)	0.70 (0.42 to 1.18)	Very Low[a,b,d]	Very uncertain

Follow-up: mean 2.3 years		1 RCT (OPRA) (29); 9,268						
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 3,167	9 per 1,000	3.4 per 1,000 (0.6 to 19.3)	5.6 fewer per 1,000 (8.4 fewer to 10,3 more)	0.38 (0.07 to 2.14)	Very Low[a,b,d]	Very uncertain
Clinical fragility fractures Follow-up: mean 2.3 years	All eligible / offer-to-screen	Females 60-80 y; 1 RCT (OPRA) (29); 9,268	96 per 1,000	75.8 per 1,000 (63.4 to 90.2)	20.2 fewer per 1,000 (32.6 fewer to 5.8 fewer)	0.79 (0.66 to 0.94)	Very Low[a-c]	Very uncertain
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 3,167	98 per 1,000	89.1 per 1,000 (63.7 to 126.4)	8.9 fewer per 1,000 (34.3 fewer to 28.4 more)	0.91 (0.65 to 1.29)	Very Low[a-d]	Very uncertain
BMD-first vs. Risk assessment-first (SCORE-based tool + BMD) screening								
Hip fractures	All eligible / offer-to-screen	Females 60-80 y;	9 per 1,000	8.5 per 1,000 (4.3 to 16.6)	0.5 fewer per 1,000	0.94 (0.48 to 1.84)	Very Low[a,b,d]	Very uncertain

Follow-up: mean 2.3 years		1 RCT (OPRA) (29); 3,926			(4.7 fewer to 7.6 more)			
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 991	8 per 1,000	3.2 per 1000 (0.5 to 22.2)	4.8 fewer per 1,000 (7.5 fewer to 14.2 more)	0.40 (0.06 to 2.78)	Very Low[a-d]	Very uncertain
Clinical fragility fractures Follow-up: mean 2.3 years	All eligible / offer-to-screen	Females 60-80 y; 1 RCT (OPRA) (29); 3,926	99 per 1,000	74.3 per 1,000 (59.4 to 91.1)	24.7 fewer per 1,000 (39.6 fewer to 7.9 fewer)	0.75 (0.60 to 0.92)	Low[a-c]	Very uncertain
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 3,167	116 per 1,000	89.3 per 1000 (59.2 to 133.4)	26.7 fewer per 1,000 (56.8 fewer to 17.4 more)	0.77 (0.51 to 1.15)	Very Low[a-d]	Very uncertain
BMD-first vs. Risk assessment-first (SOF-based tool + BMD) screening								
Hip fractures	All eligible / offer-to-screen	Females 60-80 y;	13 per 1,000	8.3 per 1000 (4.9 to 14.2)	4.7 fewer per 1,000	0.64 (0.38 to 1.09)	Very Low[a,b,d]	Very uncertain

Follow-up: mean 2.3 years		1 RCT (OPRA) (29); 7,328			(8.1 fewer to 1.2 more)			
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 2,591	9 per 1,000	3.3 per 1000 (0.5 to 19.1)	5.7 fewer per 1,000 (8.5 fewer to 10.1 more)	0.37 (0.06 to 2.12)	Very Low[a,b,d]	Very uncertain
Clinical fragility fractures Follow-up: mean 2.3 years	All eligible / offer-to-screen	Females 60-80 y; 1 RCT (OPRA) (29); 7,328	92 per 1,000	74.5 per 1000 (61.6 to 89.2)	17.5 fewer in 1,000 (30.4 fewer to 2.8 fewer)	0.81 (0.67 to 0.97)	Very Low[a-c]	Very uncertain
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 2,591	93 per 1,000	89.2 per 1000 (63.2 to 127.4)	3.8 fewer per 1,000 (29.8 fewer to 34.4 more)	0.96 (0.68 to 1.37)	Very Low[a-d]	Very uncertain
Risk assessment-first (SCORE-based tool + BMD) vs. another risk assessment-first (SOF-based tool + BMD) screening								
Hip fractures	All eligible / offer-to-screen	Females 60-80 y;	13 per 1,000	8.8 per 1000 (5.2 per 1000	4.2 fewer per 1,000	0.68 (0.40 to 1.15)	Very Low[a,b,d]	Very uncertain

Follow-up: mean 2.3 years		1 RCT (OPRA) (29); 7,282		to 15.0 per 1000)	(7.8 fewer to 2.0 more)			
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 2,752	9 per 1,000	8.2 per 1000 (3.0 to 22.7)	0.91 (0.33 to 2.52)	0.8 fewer per 1000 (6.0 fewer to 13.7 more)	Very Low[a,b,d]	Very uncertain
Clinical fragility fractures Follow-up: mean 2.3 years	All eligible / offer-to-screen	Females 60-80 y; 1 RCT (OPRA) (29); 7,282	92 per 1,000	99.4 per 1000 (84.6 to 117.8)	1.08 (0.92 to 1.28)	7.4 more per 1000 (7.4 fewer to 25.8 more)	Very Low[a-d]	Very uncertain
	Acceptors of screening	Females 60-80 y; 1 RCT (OPRA) (29); 2,752	93 per 1,000	116.3 per 1000 (88.4 to 153.5)	1.25 (0.95 to 1.65)	23.3 more per 1000 (4.6 fewer to 60.5 more)	Very Low[a-d]	Very uncertain

BMD: bone mineral density; CCT: clinical controlled trial; CI: confidence interval; RCT: randomized controlled trial; SCORE: Simple calculated osteoporosis risk estimation; SOF: Study of osteoporotic fractures (calculation); y: years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision
* The absolute effect (and its 95% CI) with risk assessment-first screening (i.e. baseline rate) is based on the estimated risk in the risk assessment-first screening group; the effect with BMD-first screening is based on applying the relative effect of the intervention (and its 95% CI) to the effect in the BMD-first group.

		KQ2: How <u>accurate</u> are screening tests at predicting fractures among adults ≥ 40 years?	

JUDGEMENT – ACCURACY OF RISK ASSESSMENT TOOLS

FRAX without BMD (lower risk of bias studies, calibrated for Canada)
- May be well-calibrated to predict 10-year hip fractures.
- Is probably well-calibrated to predict 10-year clinical fragility fractures
- May be poorly calibrated to predict 5-year hip fractures
- May be well-calibrated to predict 5-year clinical fragility fractures (most applicable to females)

FRAX with BMD (lower risk of bias studies, calibrated for Canada)
- May perform poorly to predict 10-year hip fractures.
- Is probably well calibrated to predict 10-year clinical fragility fractures
- May be well calibrated to predict 5-year hip or clinical fragility fractures (most applicable to females)

CAROC may be adequately calibrated to predict category of clinical fragility fracture risk.

Evidence for Garvan +/- BMD to predict the 10-year risk of hip or clinical fragility fractures is very uncertain. Garvan alone may underestimate the 5-year risk of hip fractures.

Evidence on QFracture is very uncertain for 10-year risk of hip and clinical fragility fracture. QFracture may underestimate 5-year hip fracture risk.

Evidence on FRISC, FRC and FRC+BMD is very uncertain.

EVIDENCE TABLES

Table 3.1 Calibration of FRAX

FRAX without BMD (high risk of bias studies)

- Evidence from high risk of bias studies (not calibrated for Canada) was very uncertain for the conclusion of poor performance to predict 10-year hip fracture
- Evidence from high risk of bias studies (n=1/12 calibrated for Canada) was very uncertain for the conclusion of poor performance to predict 10-year clinical fragility fracture
- Evidence from high risk of bias studies (not calibrated for Canada) was very uncertain for the conclusion of poor performance to predict 5-year[8] hip fracture

FRAX without BMD (lower risk of bias studies)

- FRAX without BMD (lower risk of bias studies, calibrated for Canada) may be well-calibrated to predict 10-year hip fracture.
- FRAX without BMD (lower risk of bias studies, calibrated for Canada) is probably well-calibrated to predict 10-year clinical fragility fracture.
- FRAX without BMD (lower risk of bias studies, calibrated for Canada) may be poorly-calibrated to predict 5-year hip fracture[8].
- FRAX without BMD (lower risk of bias studies, calibrated for Canada) may be well-calibrated to predict 5-year clinical fragility fracture (females only)[8].

FRAX with BMD (high risk of bias studies)

- Evidence from high risk of bias studies (not calibrated for Canada) was very uncertain for the conclusion of poor performance to predict 10-year hip for clinical fragility fracture

FRAX with BMD (lower risk of bias studies)

- FRAX with BMD (lower risk of bias studies, calibrated for Canada) may perform poorly to predict 10-year hip fracture.
- FRAX without BMD (lower risk of bias studies, calibrated for Canada) is probably well-calibrated to predict 10-year clinical fragility fracture.
- FRAX without BMD (lower risk of bias studies, calibrated for Canada) may be well-calibrated to predict 5-year hip (females)[8].
- FRAX without BMD (lower risk of bias studies, calibrated for Canada) may be well-calibrated to predict clinical fragility fracture (females only)[8].

[8] FRAX is intended for 10-year hip or major osteoporotic fracture only.

Outcome* Studies; sample size	Findings	Certainty†	What does the evidence say?	Discrimination‡ (pooled AUC, 95% CI) (5)
FRAX without BMD (high risk of bias studies)				
10-y hip fractures 13 cohort; 343,755 (30–42)	None of the FRAX tools in this analysis were calibrated for Canada. Most studies show poor calibration and are inconsistent. Most often, the tool over- (n=4 studies, 4 comparisons; O:E estimates from 0.26 to 0.72) or underestimated (n=5 studies, 7 comparisons; O:E 1.21 to 3.87) the observed fracture risk. Inconsistency was not well explained by subgroup analyses.	Very Low[a-d]	Very uncertain for the conclusion of poor performance.	All studies, regardless of risk of bias: F: 0.76 (0.72-0.81) M: 0.73 (0.68-0.77)
10-y clinical fragility fractures 12 cohort; 190,116 (30,31,41,43–46,32–34,36–40)	Only one of the 12 studies used the FRAX tool calibrated for Canada. Most studies show poor calibration and are inconsistent. Most often, the tool underestimated (n=7 studies, 8 comparisons; O:E 1.33 to 3.34) the observed fracture risk. Inconsistency was not well explained by subgroup analyses.	Very Low[a-d]	Very uncertain for the conclusion of poor performance.	All studies, regardless of risk of bias: F: 0.67 (0.65-0.68) M: 0.62 (0.61-0.64)
5-y hip fractures[8] 1 cohort; 1,054,815 (47)	A single study that did not use a FRAX tool calibrated to Canada showed underestimation of the observed 5-year risk of hip fracture (O:E 1.74, 95% CI 1.72-1.76).	Very Low[a,b,c]	Very uncertain for the conclusion of poor performance.	NR
5-y clinical fragility fractures	A single study of a FRAX tool calibrated to Canada showed overestimation of the observed 5-year risk of clinical fragility	Very Low[d]	Very uncertain for the conclusion of poor performance.	NR

Appendix 10, as supplied by the authors. Appendix to: Thériault G, Limburg H, Klarenbach S, et al. Recommendations on screening for primary prevention of fragility fractures. *CMAJ* 2023. doi: 10.1503/cmaj.221219.

		1 cohort; 9,393 (48)	fracture (O:E 0.75, 95% CI 0.68-0.89)			
		FRAX without BMD (lower risk of bias studies)				
		10-y hip fractures 3 cohort; 67,611 (43,44,46)	All studies used the FRAX tool calibrated for Canada. The pooled O:E showed acceptable calibration with some underestimation of the observed fracture risk, and a wide confidence interval **(pooled O:E 1.13, 95% CI 0.74-1.72, I^2=89.2%).**	Low[b,d]	**May be well calibrated.**	See above.
		10-y clinical fragility fractures 3 cohort; 67,611 (43,44,46)	All studies used the FRAX tool calibrated for Canada. The pooled O:E showed acceptable calibration with some underestimation of the observed fracture risk **(O:E 1.10, 95% CI 1.01-1.20, I^2=50.4%).**	Moderate[b,d]	**Probably well calibrated.**	See above.
		5-y hip fractures[8] 1 cohort; 68,730 (62,275 F, 6,445 M) (44)	A single study, which used the FRAX tool calibrated for Canada, showed large overestimation of the observed 5-year risk of hip fracture in females **(O:E 0.68, 95% CI 0.62-0.73)** and imprecise underestimation in males **(O:E 0.82, 95% CI 0.60- 1.03).**	Low[a,b,d]	**May be poorly calibrated.**	NR
		5-y clinical fragility fractures[8] 1 cohort; 68,730 (62,275 F, 6,445 M) (44)	A single study, which used the FRAX tool calibrated for Canada, found acceptable calibration in females **(O:E 0.93, 95% CI 0.89-0.96)**. The tool imprecisely underestimated the observed fracture risk in males **(O:E 1.23, 95% CI 1.08-1.38).**	Low[a,b,d]	**May be well calibrated (most applicable to females).**	NR
		FRAX + BMD (high risk of bias studies)				

There was a discordance between the effect size seen in the screening (e.g. 6.2 fewer per 1,000 (hip fractures) and treatment trials (e.g. 2.9-5.3 fewer in 1,000 hip fractures). This may be due to older population in screening trials.

See Balance of Effects section for comments on differences in population risk for hip and clinical fragility fracture compared to the Canadian general population.

10-y hip fractures 13 cohort; 138,606 (30,31,42,49,50, 32,33,36–41)	None of the FRAX tools in this analysis were calibrated for Canada. Most studies show poor calibration and are inconsistent. Most often, the tool either over- (n = 4 studies, 6 comparisons; O:E range from 0.24 to 0.68) or underestimated (n = 8 studies, 10 comparisons; O:E 1.30 to 3.33) the observed fracture risk. Inconsistency was not well explained by subgroup analyses.	Very Low[a,c,d]	Very uncertain for the conclusion of poor performance.	All studies, regardless of risk of bias: F: 0.79 (0.76-0.81) M: 0.76 (0.72-0.80)
10-y clinical fragility fractures 16 cohort; 49,235 (30,31,49–54,32,33,36–41)	None of the FRAX tools in this analysis were calibrated for Canada. Most studies show poor calibration and are inconsistent. Most often (10 studies, 12 comparisons; O:E 1.11 to 3.90), the tool underestimated the observed fracture risk. Inconsistency was not well explained by subgroup analyses.	Very Low[a-d]	Very uncertain for the conclusion of poor performance.	All studies, regardless of risk of bias: F: 0.70 (0.68-0.71) M: 0.67 (0.66-0.68)
FRAX + BMD (lower risk of bias studies)				
10-y hip fractures 3 cohort; 61,156 (43,44,46)	All studies used the FRAX tool calibrated for Canada. The pooled O:E showed underestimation of the observed risk with a high level of inconsistency (O:E 1.31, 95% CI 0.91-2.13, I^2 = 92.7%); two comparisons showed acceptable calibration while two others showed substantial underestimation of the observed fracture risk.	Low[b,d]	**May perform poorly.**	See above.
10-y clinical fragility fractures 3 cohort; 61,156 (43,44,46)	All studies used the FRAX tool calibrated for Canada. The pooled O:E showed acceptable calibration with some underestimation of the observed risk **(O:E 1.16, 95% CI 1.12-1.20, I^2 = 0%).**	Moderate[b,d]	**Probably well calibrated.**	See above.

5-y hip fractures[8] 1 cohort; 68,730 (62,275 F, 6,445 M) (44)	A single study, which used the FRAX tool calibrated for Canada, showed acceptable calibration with some overestimation in females **(O:E 0.88, 95% CI 0.81-0.95)** and males **(O:E 0.88, 95% CI 0.65-1.10).**	Low[a,b,d]	**May be well calibrated (most applicable to females.**	NR
5-y clinical fragility fractures[8] 1 cohort; 68,730 (62,275 F, 6,445 M) (44)	A single, which used the FRAX tool calibrated for Canada, study provided inconsistent findings, showing acceptable calibration in females **(O:E 1.00, 95% CI 0.97-1.04).** The tool imprecisely underestimated the observed fracture risk in males **(O:E 1.22, 95% CI 1.07, 1.37).**	Low[a,b,d]	**May be well calibrated (most applicable to females).**	NR

BMD=bone mineral density; CI=confidence interval; F=female; M=male; O:E ratio=ratio of observed to expected (predicted) events

a=risk of bias; b=inconsistency; c=indirectness; d=imprecision

*Rows for 5-year fractures have been omitted from the table when no studies were located that reported on this outcome.

† When our assessment of the certainty of evidence fell between levels, we assigned the level that best represented our actual certainty.

‡Extracted directly from the 2018 USPSTF systematic review by Viswanathan et al. (5).

Table 3.2 Calibration of CAROC

- CAROC: may be adequately calibrated to predict category of clinical fragility fracture risk (one study only)

CAROC (includes BMD)				
10-y hip fractures	No studies reported this outcome.	Not applicable		NR
10-y clinical fragility fractures 1 cohort; 34,060 (55)	One study did not report an O:E ratio. Observed fracture risk (95% CI) was 6.4 (6.0-6.8)% in the low risk (<10%) group, 13.8 (13.1-14.5)% in the moderate risk group (10-20%), and 23.8 (22.5-25.0)% in the high risk group (>20%).	Low[a-c]	**May be adequately calibrated to predict a category of risk.**	NR

BMD=bone mineral density; CI=confidence interval; F=female; M=male; O:E ratio=ratio of observed to expected (predicted) events a=risk of bias; b=inconsistency; c=indirectness; d=imprecision

*Rows for 5-year fractures have been omitted from the table when no studies were located that reported on this outcome.

† When our assessment of the certainty of evidence fell between levels, we assigned the level that best represented our actual certainty.

‡Extracted directly from the 2018 USPSTF systematic review by Viswanathan et al. (5).

Table 3.3 Calibration of Garvan, QFracture, FRISC and FRC

- Evidence on using Garvan +/- BMD to predict the 10-year risk of hip or clinical fragility fractures is very uncertain.
- Garvan alone may underestimate the 5-year risk of hip fractures.
- Evidence on QFracture is very uncertain for 10-year risk of hip and clinical fragility fracture. QFracture may underestimate 5-year hip fracture risk.
- Evidence on FRISC (Fracture and Immobilization Score (includes BMD)), FRC (Fracture Risk Calculator) and FRC+BMD is very uncertain.

Garvan alone (no BMD)				
10-y hip fractures 2 cohort; 67,923 (46,56)	In one study, the tool substantially underestimated the observed fracture risk (O:E 3.63, 95% CI 3.31-3.97). A second study reported only the Hosmer-Lemeshow test (p<0.0001), indicating poor calibration.	Very Low[a-c]	Very uncertain for the conclusion of poor performance	F: 0.68 (NR) F: 0.65 (NR)
10-y clinical fragility fractures 1 cohort; 5,063 (56)	In one study, the Hosmer-Lemeshow test was significant (p=0.01014), indicating poor calibration.	Very Low[a,b]	Very uncertain for the conclusion of poor performance	F: 0.66 (0.61-0.72) M: NR
5-y hip fractures 1 cohort; 1,054,815 (47)	In one study, the tool substantially underestimated the observed fracture risk (O:E 2.17, 95% CI 2.16-2.17).	Low[a-c]	**May underestimate by 116 to 117%**	NR

		Garvan + BMD				
		10-y hip fractures 5 cohort; 11,869 (31,40,56–58)	Most studies show poor calibration and are inconsistent. Most often, the tool overestimated fracture risk to an important magnitude, though the degree of overestimation is highly variable (n = 3 studies, 4 comparisons, O:E 0.10 to 0.66). Inconsistency was not well explained by subgroup analyses.	Very Low[a,b,d]	Very uncertain for the conclusion of poor performance	F: 0.73 (0.66-0.79) M: 0.79 (NR)
		10-y clinical fragility fractures 5 cohort; 11,733 (31,40,56–58)	Most studies show poor calibration and are inconsistent. Most often, the tool over- (n = 2 studies, 2 comparisons; O:E 0.34 to 0.74) or underestimated (n = 1 study, 1 comparison; O:E 1.65) the observed fracture risk. One study reported only the Hosmer-Lemeshow test (p=0.0001), indicating poor calibration. Inconsistency was not well explained by subgroup analyses.	Very Low[a,b,d]	Very uncertain for the conclusion of poor performance	F: 0.68 (0.64-0.71) M: 0.75 (NR)
		QFracture (no BMD)				
		10-y hip fractures 1 cohort; 5,200 (56)	In one study, the O:E was not reported. The Hosmer-Lemeshow test was significant (p<0.0001), indicating poor calibration.	Very Low[a,b,d]	Very uncertain for the conclusion of poor performance	NR
		10-y clinical fragility fractures 1 cohort; 5,063 (56)	In one study, the O:E was not reported. The Hosmer-Lemeshow test was significant (p=0.0001), indicating poor calibration	Very Low[a,b,d]	Very uncertain for the conclusion of poor performance	NR

5-y hip fractures 1 cohort; 1,054,815 (47)	In one study, the tool underestimated the observed fracture risk (O:E 1.42, 95% CI 1.41-1.42).	Low[a-c]	**May underestimate by 40 to 42%**	NR
Fracture and Immobilization Score (FRISC; includes BMD)				
10-y hip fractures	No studies reported this outcome.	Not applicable		NR
10-y clinical fragility fractures 1 cohort; 400 (52)	In one study, FRISC was imprecise for overestimation of the 10- year risk of clinical fragility fracture (O:E 0.74, 95% CI 0.59-0.93)	Very Low[a,b,d]	Very uncertain for the conclusion of poor performance	F: 0.73 (NR)
Fracture Risk Calculator (FRC) alone (no BMD)				
10-y hip fractures 2 cohort; 100,382 (59,60)	The evidence from 2 cohort studies (n=100,382) is very uncertain.	Very Low[a-d]	Very uncertain for the conclusion of poor performance	F: 0.83 (0.82-0.84) M: 0.71 (NR)
10-y clinical fragility fractures 1 cohort; 5,893 (59)	The evidence from 1 cohort study (n=5,893) is very uncertain.	Very Low[a-d]	Very uncertain for the conclusion of poor performance	F: NR M: 0.66 (NR)
FRC + BMD				
10-y hip fractures 2 cohort; 100,382 (59,60)	The evidence from 2 cohort studies (n=100,382) is very uncertain.	Very Low[a-d]	Very uncertain for the conclusion of poor performance	F: 0.85 (0.84-0.86) M: 0.79 (NR)

10-y clinical fragility fractures 1 cohort; 5,893 (59)	The evidence from 1 cohort study (n=5,893) is very uncertain.	Very Low[a-d]	Very uncertain for the conclusion of poor performance	F: NR M: 0.70 (NR)	

BMD=bone mineral density; CI=confidence interval; F=female; M=male; O:E ratio=ratio of observed to expected (predicted) events

a=risk of bias; b=inconsistency; c=indirectness; d=imprecision

*Rows for 5-year fractures have been omitted from the table when no studies were located that reported on this outcome.

† When our assessment of the certainty of evidence fell between levels, we assigned the level that best represented our actual certainty.

‡Extracted directly from the 2018 USPSTF systematic review by Viswanathan et al. (5).

KQ3a. What are the benefits of pharmacologic treatments to prevent fragility fractures among adults ≥40 years?

JUDGEMENT – BENEFITS OF TREATMENT

Bisphosphonates (as a class) and risedronate may reduce hip fractures in post-menopausal females.

Bisphosphonates (as a class), alendronate, zoledronic acid and denosumab probably reduce clinical fragility fractures in post-menopausal females. Risedronate may reduce clinical fragility fractures in post-menopausal females.

Bisphosphonates (as a class) and zoledronic acid may reduce clinical vertebral fractures in post-menopausal females.

Bisphosphonates as a class may not reduce the risk of all-cause mortality compared to placebo over 1 to 6 years of follow-up (post-menopausal females). Evidence for individual bisphosphonates is very uncertain for all-cause mortality.

Evidence for males (zoledronic acid or denosumab) is very uncertain.

EVIDENCE TABLES

Table 4.1 Benefits of treatment

Bisphosphonates (as a class, post-menopausal females)

		- Treatment with **bisphosphonates** as a class **may reduce the risk of hip fractures** (2.9-5.3 fewer in 1,000), **probably reduces the risk of clinical fragility fractures** (11.1-33.6 fewer in 1,000) and it **may reduce clinical vertebral fractures** (10.0-12.8 fewer in 1,000). Treatment with bisphosphonates may not reduce all-cause mortality. Alendronate (post-menopausal females) - Alendronate may not reduce hip fractures. - **Alendronate probably reduces clinical fragility fractures** (14.7-28.4 fewer in 1,000). Evidence for clinical vertebral fractures and all-cause mortality was uncertain. Risedronate (post-menopausal females) - **Risedronate may reduce hip fractures** (5.3-7.9 fewer in 1,000) **and clinical fragility fractures** (7.8-28.4 fewer in 1000). Evidence for clinical vertebral fractures and all-cause mortality was uncertain. Zoledronic acid (post-menopausal females) - Zoledronic acid may not reduce hip fractures. - **Zoledronic acid probably reduced clinical vertebral fractures** (20.1-62.6 fewer in 1,000) and **may reduce clinical vertebral fractures** (14.9-18.7 fewer in 1000). Evidence for all-cause mortality was uncertain. Zoledronic acid (men) - Zoledronic acid may not reduce hip fractures and clinical fragility fractures. - The evidence for all-cause mortality was very uncertain Denosumab (post-menopausal females) - Denosumab may not reduce hip fractures - **Denosumab probably reduces the risk of clinical fragility fractures** (12.2-51.5 fewer in 1,000) **and clinical vertebral fractures** (16.2-18.2 fewer in 1,000). - Denosumab probably does not reduce all-cause mortality and probably does not change health-related quality of life. Denosumab (men) - The evidence for hip, clinical fragility and clinical vertebral fractures, and all-cause mortality was very uncertain.	

Outcome & Study approach	Studies; sample size; follow-up	Anticipated absolute effects (95% CI)			Relative OR (95% CI)	Certainty	Judgement
		Assumed population risk*	Risk with treatment	Absolute difference			
Bisphosphonates (alendronate, risedronate or zoledronic acid) vs placebo (postmenopausal females)							
Hip fractures Intention to treat	14 RCT; 21,038 Follow-up: 12-72 months (61–76)	Study data: 11 in 1000	8.1 per 1,000 (6.4 t 10.1)	**2.9 fewer in 1000 (4.6 fewer to 0.9 fewer)**	0.73 (0.58 to 0.92)	Low[a,c]	**May reduce**
		General F ≥65 y: 20 in 1000	14.7 per 1,000 (11.7 to 18.4)	**5.3 fewer in 1000 (8.3 fewer to 1.6 fewer)**			
Clinical fragility fractures Intention to treat or exposed to ≥1 dose	19 RCT; 22,482 Follow-up: 12-72 months (61,63,73–82,64,83–85,65–71)	Study data: 58 in 1000	46.9 per 1,000 (43.0 to 51.4)	**11.1 fewer in 1000 (15.0 fewer to 6.6 fewer)**	0.80 (0.73 to 0.88)	Moderate[a,c]	**Probably reduces**
		General F ≥65 y: 202 in 1000	168.4 per 1,000 (156.0 to 182.2)	**33.6 fewer in 1000 (46.0 fewer to 19.8 fewer)**			
Clinical vertebral fractures; Intention to treat or exposed to ≥1 dose	11 RCT; 8,921 Follow-up: 12-72 months (61,62,80,82,85,63–69,72)	Study data: 21 in 1000	11.0 per 1000 (7.0 to 17.1)	**10.0 fewer in 1000 (14.0 fewer to 3.9 fewer)**	0.52 (0.33, 0.81)	Low[a,b,d]	**May reduce**
		General F ≥65 y: 27 in 1000	14.2 per 1000 (9.1 to 22.0)	**12.8 fewer in 1000 (17.9 fewer to 5.0 fewer)**	0.52 (0.33, 0.81)		

All-cause mortality Intention to treat or exposed to ≥1 dose	8 RCT; 8,542 Follow-up: 12-72 months (62–64,67,68,72,81,84,86)	Study data: 30 in 1000	24.0 per 1,000 (17.6 to 32.9)	5.5 fewer in 1000 (11.9 fewer to 3.4 more)	0.81 (0.59 to 1.12)	Low[a-c]	**May not reduce**	
		General F >65 y: 57 in 1000	46.7per 1,000 (34.4 to 63.4)	10.3 fewer in 1000 (22.6 fewer to 6.4 more)				
Alendronate vs placebo (post-menopausal females)								
Hip fractures Intention to treat	7 RCT; 9,226 post-menopausal Females Follow-up: 12-48 months (61,62,68–73)	Study data: 8 in 1000	5.9 per 1000 (3.5 to 9.9)	2.1 fewer in 1000 (4.5 fewer to 1.9 more)	0.73 (0.43, 1.24)	Low[b,c,d]	**May not reduce**	
		General F ≥65 y: 20 in 1000	5.9 per 1000 (3.5 to 9.9)	5.3 fewer in 1000 (11.3 fewer to 4.7 more)	0.73 (0.43, 1.24)			
Clinical fragility fractures Intention to treat	8 RCT; 8,854 post-menopausal females Follow-up: 12-48 months (61,68,81,69–71,73,77–80)	Study data: 96 in 1000	79.3 per 1000 (69.5 to 91.4)	**14.7 fewer in 1000 (24.5 fewer to 2.6 fewer)**	0.83 (0.72, 0.97)	Moderate[b,c]	**Probably reduces**	
		General F ≥65 y: 202 in 1000	173.6 per 1000 (154.2 to 197.1)	**28.4 fewer in 1000 (47.8 fewer to 4.9 fewer)**	0.83 (0.72, 0.97)			

Clinical vertebral fractures	The evidence from (n=6,324, follow-up: 12-48 months) is very uncertain is very uncertain (61,62,68,69,72,80).					Very Low[a-d]	Very uncertain
All-cause mortality	The evidence from 4 RCTs (n=5,272, follow-up: 12-48 months) is very uncertain (62,68,72,81,86).					Very Low[b,c]	Very uncertain
Risedronate vs placebo (post-menopausal females)							
Hip fractures Intention to treat	4 RCT; 9,672 post-menopausal females Follow-up: 12-36 months (63,74–76)	Study data: 30 in 1000	22.1 per 1000 (17.0 to 28.5)	**7.9 fewer in 1000** **(13.0 fewer to 1.5 fewer)**	0.73 (0.56 to 0.95)	Low[b,c]	**<u>May reduce</u>**
		General F ≥65 y: 20 in 1000	14.7 per 1000 (11.3 to 19.0)	**5.3 fewer in 1000** **(8.7 fewer to 1.0 fewer)**	0.73 (0.56 to 0.95)		
Clinical fragility fractures Intention to treat or exposed to ≥1 dose	7 RCT; 10,572 post-menopausal females Follow-up: 12-36 months (63,74–76,78,82,83)	Study data: 48 in 1000	40.2 per 1000 (35.5 to 45.7)	**7.8 fewer in 1000** **(12.5 fewer to 2.3 fewer)**	0.83 (0.73, 0.95)	Low[a-c]	**<u>May reduce</u>**
		General F ≥65 y: 202 in 1000	173.6 per 1000 (156.0 to 193.9)	**28.4 fewer in 1000** **(46.0 fewer to 8.1 fewer)**	0.83 (0.73, 0.95)		
Clinical vertebral fractures	The evidence from 2 RCTs (n=230, follow-up: 12-24 months) is very uncertain (63,82).					Very Low[a,c,d]	Very uncertain
All-cause mortality	The evidence from 1 RCT (n=170, follow-up: 12 months) is very uncertain (63).					Very Low[a,b,d]	Very uncertain

Zoledronic acid vs placebo (post-menopausal females)								
Hip fractures Intention to treat	3 RCT; 2,200 Follow-up: 12-72 months (64–67)	Study data: 12 in 1000	8.3 per 1,000 (3.5 to 19.4)	3.7 fewer in 1000 (8.5 fewer to 7.4 more)	0.69 (0.29 to 1.63)	Low[b,c]	May not reduce
		General F ≥65 y: 20 in 1000	13.9 per 1,000 (5.9 to 32.2)	6.1 fewer in 1000 (14.1 fewer to 12.2 more)			
Clinical fragility fractures Intention to treat	5 RCT; 3,218 Follow-up: 12-72 months (64–67,84,85)	Study data: 50 in 1000	37.9 per 1,000 (30.4 to 48.1)	20.1 fewer in 1000 (27.6 fewer to 9.9 fewer)	0.64 (0.51 to 0.82)	Moderate[b]	Probably reduces
		General F ≥65 y: 202 in 1000	139.4 per 1,000 (114.3 to 171.9)	62.6 fewer in 1000 (87.7 fewer to 30.1 fewer)			
Clinical vertebral fractures Intention to treat	4 RCT; 2,367 Follow-up: 12-72 months (64–67,85)	Study data: 34 in 1000	15.3 per 1,000 (8.4 to 27.4)	18.7 fewer in 1000 (25.6 fewer to 6.6 fewer)	0.44 (0.24 to 0.8)	Low[a,b,d]	May reduce
		General F ≥65 y: 27 in 1000	12.1 per 1,000 (6.6 to 21.7)	14.9 fewer in 1000 (20.4 fewer to 5.3 fewer)			
All-cause mortality	The evidence from 3 RCTs (n=2,656, follow-up=12-72 months) is very uncertain (64,67,84)					Very Low[a,b,c,d]	Very uncertain
Zoledronic acid vs placebo (men)							

Hip fractures Intention to treat	1 RCT; 1,199 Follow-up: 24 months (87)	Study data: 2 in 1000	4.2 per 1,000 (0.4 to 44.0)	2.2 more in 1000 (1.6 fewer to 42.0 more)	2.08 (0.19 to 22.98)	Low[b,c]	May not reduce
		General M ≥65 y: 16 in 1000	32.7 per 1,000 (3.1 to 272.0)	16.7 more in 1000 (12.9 fewer to 256.0 more)			
Clinical fragility fractures Intention to treat	1 RCT; 1,199 Follow-up: 24 months (87)	Study data: 18 in 1000	10.3 per 1,000 (3.8 to 27.5)	7.7 fewer in 1000 (14.2 fewer to 9.5 more)	0.57 (0.21 to 1.54)	Low[b,d]	May not reduce
		General M ≥65 y: 105 in 1000	62.7 per 1,000 (24.0 to 153.0)	42.3 fewer in 1000 (81.0 fewer to 48.0 more)			
Clinical vertebral fractures	No study reported on this outcome.						
All-cause mortality	The evidence from 1 RCT (n=1,199, follow-up=24 months) is very uncertain (87).					Very Low[a,b,d]	Very uncertain
Denosumab vs placebo (post-menopausal females)							
Hip fractures Intention to treat	3 RCT; 8,542 Follow-up: 6-36 months	Study data: 11 in 1000	7.1 per 1,000 (4.3 to 11.2)	3.9 fewer in 1000 (6.7 fewer to 0.2 more)	0.64 (0.39 to 1.02)	Low[b-d]	**May not reduce**

	(88–92)	General F ≥65 y: 20 in 1000	12.9 per 1,000 (7.9 to 20.4)	7.1 fewer in 1000 (12.1 fewer to 0.4 more)			
Clinical fragility fractures Intention to treat or exposed to ≥1 dose	5 RCT; 9,231 Follow-up: 12-36 months (81,86,88–91,93)	Study data: 42 in 1000	29.8 per 1,000 (25.2 to 34.7)	**12.2 fewer in 1000 (16.8 fewer to 7.3 fewer)**	0.70 (0.59 to 0.82)	Moderate[b]	**Probably reduces**
		General F ≥65 y: 202 in 1000	150.5 per 1,000 (129.9 to 171.9)	**51.5 fewer in 1000 (72.1 fewer to 30.1 fewer)**			
Clinical vertebral fractures Intention to treat or exposed to ≥1 dose	3 RCT; 8,397 Follow-up: 6-36 months (88,91,93–95)	Study data: 24 in 1000	7.8 per 1,000 (5.1 to 11.9)	**16.2 fewer in 1000 (18.9 fewer to 12.1 fewer)**	0.32 (0.21 to 0.49)	Moderate[b]	**Probably reduces**
		General F ≥65 y: 27 in 1000	8.8 per 1,000 (5.8 to 13.4)	**18.2 fewer in 1000 (21.2 fewer to 13.6 fewer)**			
All-cause mortality Intention to treat or exposed to ≥1 dose	5 RCT; 9,185 Follow-up: 6-36 months (81,86,88–91,93,95)	Study data: 23 in 1000	18.3 per 1,000 (13.5 to 24.8)	4.7 fewer in 1000 (9.5 fewer to 1.8 more)	0.79 (0.58 to 1.08)	Moderate[b,d]	**Probably does not reduce**
		General F >65 y: 57 in 1000	45.6 per 1,000 (33.9 to 61.3)	11.4 fewer in 1000 (23.1 fewer to 4.3 more)			

Health-related quality of life (OPAQ-SV; 0-100; higher = better) after 3-y of treatment	1 RCT; 6,481 Follow-up: 36 months (96)	Change from baseline: physical function (-1.3 vs. -1.2), emotional status (-1.4 vs. -1.6), and back pain (4.1 vs. 4.3) for denosumab vs. placebo.				Moderate[b,c]	**Probably does not change**
Denosumab vs placebo (men)							
Hip fractures Intention to treat	1 RCT; 242 Follow-up: 12 months (97)	Study data: 0 in 1000	0.0 per 1,000 (0 to 0)	No difference in 1000	1.00 (0.02 to 50.80)	Very low[a,b,d]	Very uncertain
		General M ≥65 y: 16 in 1000	16.0 per 1,000 (0.3 to 452.4)	No difference in 1000 (15.7 fewer to 436.4 more)			
Clinical fragility fractures Intention to treat	1 RCT; 242 Follow-up: 12 months (97)	Study data: 16 in 1000	8.6 per 1,000 (0.7 to 88.2)	8.4 fewer in 1000 (16.3 fewer to 71.2 more)	0.50 (0.04 to 5.59)	Very low[a,b,d]	Very uncertain
		General M ≥65 y: 105 in 1000	55.4 per 1,000 (4.7 to 396.1)	49.6 fewer in 1000 (100.3 fewer to 291.1 more)			
Clinical vertebral fractures Intention to treat	1 RCT; 242 Follow-up: 12 months (97)	Study data: 0 in 1000	0.0 per 1,000 (0.0 to 0.0)	No difference in 1000	1.00 (0.02 to 50.80)	Very low[a,b,d]	Very uncertain
		General M ≥65 y: 10 in 1000	10.0 per 1,000 (0.2 to 339.1)	No difference in 1000 (9.8 fewer to 329.1 more)			

		All-cause mortality Exposed to ≥1 dose	1 RCT; 240 Follow-up: 12 months (97)	Study data: 8 in 1000	8.0 per 1,000 (0.5 to 115.4)	No difference in 1000 (7.5 fewer to 107.4 more)	1.00 (0.06 to 16.17)	Very low[a,b,d]	Very uncertain	
				General M >65 y: 76 in 1000	76.0 per 1,000 (4.9 to 570.8)	No difference in 1000 (71.1 fewer to 494.8 more)				
		CI=confidence interval; RCT=randomized controlled trial; NA=not applicable; OPAQ-SV=Osteoporosis Assessment Questionnaire-Short Version; y=years a=risk of bias; b=inconsistency; c=indirectness; d=imprecision * The effects without screening for the general risk population are estimated from Prior et al. based on 10 year follow-up (28). Data for the general population <65 years is not included in the summary table.								
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○Large **X** Small ○Moderate ○Trivial ○Varies ○Don't know	**KQ1a: What are the <u>harms</u> of screening compared with no screening to prevent fragility fractures and related morbidity and mortality in primary care for adults ≥ 40 years?**								

JUDGEMENT – HARMS OF SCREENING

Selected Populations[9]: (Offer-to-screen, females ≥65 years)
The evidence for serious adverse events was very uncertain.
(See KQ3b for further harms of treatment)
Overdiagnosis: Screening resulted in 11.8% (using 10-year hip fracture risk) and 19.3% (using 10-year MOF[10] risk) being identified as high risk that would never have known they were at risk and would never have experienced a fracture. This overdiagnosis may result in labelling, anxiety and/or unnecessary treatment.

Selected Populations[9]: (Acceptors of screening, females 70-85 years)
Overdiagnosis: Screening resulted in 24.1% being overdiagnosed using 10-year hip fracture risk.

EVIDENCE TABLES

Table 5.1 Harms of Screening (Serious adverse events)

- The evidence about serious adverse events in offer-to-screen in selected populations (females 70-85 y) is very uncertain.

Outcome	Study approach	Population Studies; Sample size	Findings	Certainty	Judgement
Serious adverse events	Offer-to-screen in selected[9] population Follow-up: 5 years	Females 70-85 y; 1 RCT (SCOOP)(26); 12,483	No serious adverse events reported	Very Low to Low[a,b,d]	Very uncertain

RCT: randomized controlled trial; y: years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision

Table 5.2 Harms of Screening (Overdiagnosis)

- For those ***offered screening in selected populations[9]*, 11.8%** (females 70-85 y, using 10-year hip fracture risk) and **19.3%** (females 65-90 y, using 10-year MOF[10] risk may be identified as high risk that would never have known they were at risk and would never experienced a fracture. For those who ***accepted screening in selected populations[9]*, 29%** (females 70-85 y, using 10-year hip fracture risk) may be identified as high risk that would never have known they were at risk and would never experienced a fracture.

Outcome	Study approach	Population Studies; Sample size	Findings	Certainty
Overdiagnosis	Offer-to-screen in selected[9] populations	Females 70-85 y; 1 RCT (SCOOP) (26); 6,233	14.4 x (100-17.9) /100 = **11.8% overdiagnosed** (using 10-year hip fracture risk)	Low[c]
		Females 65-90 y; 1 RCT (SALT) (25); 5,575	25.4 x (100-23.9) / 100 = **19.3% overdiagnosed**	Low[c]

[9] Females ≥65 years willing to independently complete a mailed fracture risk questionnaire.
[10] MOF=Major osteoporotic fracture.

			(using 10-year MOF risk)	
	Acceptors of screening in selected[g] populations	Females 70-85 y; 1 RCT (SCOOP) (26); 2,750	29.3 x (100-17.9) / 100 = **24.1% overdiagnosed** (using 10-year hip fracture risk)	Low[c]

RCT: randomized controlled trial; y: years
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision

KQ3b. What are the harms of pharmacologic treatments to prevent fragility fractures among adults ≥40 years?

JUDGEMENT – HARMS OF TREAMENT

Serious harms

Bisphosphonates (as a class) and alendronate may increase rare but serious harms of subtrochanteric atypical femoral fracture and osteonecrosis of the jaw.

The risk of 'any serious adverse event' (composite outcome) is probably not increased with risedronate and zoledronic acid and may not be increased with alendronate.

The risk of certain serious gastrointestinal (GI) adverse events (perforations, ulcers, and bleeds; serious esophageal) may not be increased with alendronate.

The risk of stroke and myocardial infarction probably does not increase with bisphosphonates (as a class); and the risk of other serious cardiovascular events may not increase with alendronate, zoledronic acid and denosumab.

Non-serious harms

Alendronate and denosumab probably increase non-serious GI adverse events.

Zoledronic acid probably increases any non-serious adverse event (AE), pyrexia, headache, influenza-like symptoms, arthritis and arthralgia, myalgia and may increase the composite measure of arthralgia, myalgia, pyrexia, chills, & influenza-like symptoms.

Denosumab probably increases rash/eczema and infections and may increase eczema alone.

EVIDENCE TABLES

Table 6.1 Harms of Treatment (Alendronate)

- Alendronate may increase subtrochanteric atypical femoral fractures (0.06-0.08 more per 1,000) and osteonecrosis of the jaw (0.22 more per 1,000).
- Alendronate may not increase the composite "any serious AE", the composite "GI perforations, ulcers, or bleeds", serious esophageal AEs or atrial fibrillation.
- Alendronate probably increases non-serious GI events (16.3 more per 1,000) but probably does not increase discontinuation due to AE and may not increase the composite measure of any non-serious AE.
- Evidence for serious GI (any), GI cancer, serious cardiovascular AE and atypical femoral fractures (any, with treatment >3 years) was uncertain.

Outcome	Studies; sample Size	Assumed pop. risk*	Absolute effects (95% CI)	Relative RR unless otherwise stated (95% CI)	Certainty	Judgement
Alendronate vs. placebo or no treatment						
Serious adverse events						
Atypical femoral fractures (subtrochanteric) (99)	1 cohort; 220,360	0.06 per 1000	**0.08 more per 1000 (0.05 more to 0.14 more)**	**HR** 2.41 (1.78 to 3.27)	Low[a,b,e]	**May increase**
Atypical femoral fractures (femoral shaft) (99)	1 cohort; 220,360	0.03 per 1000	**0.06 more per 1000 (0.03 more to 0.10 more)**	**HR** 2.90 (1.97 to 4.26)	Low[a,b,e]	**May increase**
Osteonecrosis of the jaw (99)	1 cohort; 220,360	0.1 per 1000	**0.22 more per 1000 (0.04 more to 0.59 more)**	**HR** 3.15 (1.44 to 6.87)	Low[a,b,e]	
Any serious AE) (5,100)	5 RCT; 1,955	106 per 1000	5.7 fewer per 1000 (31.9 fewer to 29.4 more)	0.95 (0.71 to 1.27)	Low[a,b]	**May not increase**
GI perforations, ulcers, bleeds (2,101,102)	10 RCT; 137 Events	NR	Cannot be calculated; NS difference	0.89 (0.63 to 1.25)	Low[a,b]	

Serious esophageal AE (100–102)	5 RCT; 499,062	NR	Cannot be calculated; NS difference	1.39 (0.75 to 2.65)	Low[a,b,d]	
Atrial fibrillation (100–102)	1 RCT; NR	14 per 1000	3.6 more per 1000 (0.6 fewer to 9.0 more)	**OR** 1.26 (0.96 to 1.66)[†]	Low[a,b]	
	1 SR of 32 RCT; 17,291		2.2 more per 1000 (1.8 fewer to 7.7 more)			
Very uncertain: Serious GI AEs (any) [a,b,d] (2,101,102), GI cancer (colorectal[b,], gastric[d], esophageal[b,d], liver[b], pancreatic[d], oral[b,d], bile duct[b,d], small intestinal[b,d]) (103), serious cardiovascular AE (acute coronary syndrome[a,b,d], cerebrovascular death[ra,b,d], thromboembolic events[a,b,d]) (2,101,102), and atypical femoral fractures (any[b,d], with long term treatment [>3 years][a,b]) (99). No evidence: serious stroke, pulmonary embolism.						
Non-serious adverse events and discontinuation due to AE						
Non-serious GI AE (2,101,102)	50 RCT; 22,549	589 per 1000	**16.3 more per 1000 (2.4 more to 31.3 more)**	**OR** 1.07 (1.01 to 1.14)[‡]	Moderate[a]	**Probably increases**
Discontinuation due to AE (5,100)	9 RCT; 9,160	68 per 1000	1.4 fewer per 1000 (10.0 fewer to 8.3 more)	0.98 (0.85 to 1.12)	Moderate[a]	**Probably does not increase**
Any non-serious AE (104)	5 RCT; 4,720	815 per 1000	16.3 fewer per 1000 (81.5 fewer to 48.9 more)	0.98 (0.90 to 1.06)	Low[a,b]	**May not increase**
Very uncertain: Influenza-like symptoms[a,b,d] (104), and musculoskeletal (arthritis and arthralgia[a,b,d]; myalgia, cramps, and limb pain[a,b,d]) AEs (2,101,102).						

AE=adverse event; GI=gastrointestinal; NR=not reported; NS=not statistically significant; RCT=randomized controlled trial; SR=systematic review

*The control event rate is the median rate in the control group for studies in the analysis. These were extracted directly from the systematic reviews when possible. Otherwise, we extracted these data from the included primary studies when there were ≤5 in the analysis or used the 5 largest studies from larger analyses to calculate the control event rate.

a=risk of bias; b=inconsistency; c=indirectness; d=imprecision; e=Large magnitude of effect (+1)

[†]The absolute effect (and its 95% CI) without treatment (i.e. baseline rate) is based on the estimated risk in the comparison group; the effect with treatment is based on applying the relative effect of the intervention (and its 95% CI) to the effect without treatment. When an OR is presented, we used the following formula recommended in the Cochrane manual: intervention risk per 1000 = 1000 x (OR x ACR / 1 – ACR + (OR x ACR))

[‡]Odds ratio derived from exact logistic regression meta-analysis (101).

Table 6.2 Harms of Treatment (Risedronate)

- Risedronate probably does not increase any serious AE, any non-serious AE, any non-serious GI AE or discontinuation due to AEs.
- Evidence for influenza-like symptoms, pharyngitis, and arthritis or arthralgia was very uncertain.

Outcome	Studies; sample size	Assumed pop. risk*	Absolute effects (95% CI)	Relative RR unless otherwise stated (95% CI)	Certainty	Judgement
Risedronate vs. placebo						
Serious adverse events						
Any serious AE (5,100)	5 RCT; 7,195	11 per 1000	2.6 fewer per 1000 (10.2 fewer to 5.7 more)	0.98 (0.91 to 1.05)	Moderate[a]	**Probably does not increase**
Very uncertain: serious GI AEs (all[a,c]; GI perforations, ulcers bleeds[a,b,d]; serious esophageal AE[a,b,d]) (2,101,102), GI cancer[a,b,d] (2,101,102), acute coronary syndrome[a,b,d], cerebrovascular death[a,b,d], pulmonary embolism[a,b,d] (2,101,102), atrial fibrillation[a,b,d] (2,101,102). No evidence: serious stroke, thromboembolic events (2,101,102), atypical femoral fractures, or osteonecrosis of the jaw.						
Non-serious adverse events and discontinuation due to AE						
Any non-serious AE (104)	6 RCT; 9,575	915 in 1000	45.8 fewer in 1000 (146.4 fewer to 73.2 more)	0.95 (0.84 to 1.08)	Moderate[a]	**Probably does not increase**
Non-serious GI AE (2,101,102)	21 RCT; 3,474 Events	223 in 1000	5.2 more in 1000 (8.8 fewer to 20.3 more)	**OR** 1.03 (0.95 to 1.12)[‡]	Moderate[a]	
Discontinuation due to AE (5,100)	5 RCT; 7,159	111 in 1000	1.0 fewer in 1000 (11.8 fewer to 10.9 more)	0.99 (0.89 to 1.10)	Moderate[a]	
Very uncertain: influenza-like symptoms[a,b,d] (104), pharyngitis[a,b,d] (104), and arthritis and arthralgia[a,b,d] (2,101,102). No evidence: myalgia, cramps, and limb pain (2,101,102)						

AE=adverse event; GI=gastrointestinal; NR=not reported; NS=not statistically significant; RCT=randomized controlled trial; SR=systematic review

* The control event rate is the median rate in the control group for studies in the analysis. These were extracted directly from the systematic reviews when possible. Otherwise, we extracted these data from the included primary studies when there were ≤5 in the analysis or used the 5 largest studies from larger analyses to calculate the control event rate.

a=risk of bias; b=inconsistency; c=indirectness; d=imprecision; e=Large magnitude of effect (+1)

‡Odds ratio derived from exact logistic regression meta-analysis (101).

Table 6.3 Harms of Treatment (Zoledronic acid)

- Zoledronic acid probably does not increase any serious AE and may not increase acute coronary syndrome, serious stroke, or non-serious GI AEs.
- Evidence for cerebrovascular death, atrial fibrillation, atypical femoral fractures and osteonecrosis of the jaw was very uncertain.
- Zoledronic acid probably increases the composite of "any non-serious AE", pyrexia, headache, influenza-like symptoms, arthritis and arthralgia, myalgia, the composite of arthralgia, myalgia, pyrexia, chills and flu-like symptoms, and chills
- Zoledronic acid may not increase non-serious GI AEs
- The evidence for discontinuation due to AEs is very uncertain

Outcome	Studies; sample size	Assumed pop. risk*	Absolute effects (95% CI)	Relative RR unless otherwise stated (95% CI)	Certainty	Judgement
Zoledronic acid vs. placebo						
Serious adverse events						
Any serious AE (5,100)	3 RCT; 1,950	114 in 1000	0.9 fewer in 1000 (19.8 fewer to 21.8 more)	0.99 (0.83 to 1.19)	Moderate[a]	**Probably does not increase**
Acute coronary syndrome (2,101,102)	2 RCT; NR	NR	Cannot be calculated; NS difference	**OR** 0.82 (0.55 to 1.21)[‡]	Low[a,b,d]	**May not increase**
Serious stroke (2,101,102)	2 RCT; NR	NR	Cannot be calculated; NS difference	**OR** 1.13 (0.90 to 1.42)[‡]	Low[a,b,d]	
Very uncertain: cerebrovascular death[a,b,d] (2,101,102), atrial fibrillation[a,d] (2,101,102), atypical femoral fractures[a,b,d] (2,101,102), osteonecrosis of the jaw[a,b,d] (2,101,102). No evidence: serious GI AE (any; GI perforations, ulcers, bleeds; serious esophageal AE), GI cancer, pulmonary embolism, thromboembolic events.						
Non-serious adverse events and discontinuation due to AE						
Any non-serious AE (104)	6 RCT; 9,575	915 in 1000	**51.8 more per 1000 (no difference to 112.2 more)**	1.06 (1.00 to 1.13)	Moderate[a]	**Probably increases**
Pyrexia (104)	5 RCT; 11,823	38 in 1000	**127.7 more in 1000 (34.6 more to 337.4 more)**	4.36 (1.91 to 9.88)	Moderate[a]	
Headache (104)	4 RCT; 9,712	53 in 1000	**60.4 more in 1000 (19.1 more to 126.7 more)**	2.14 (1.36 to 3.39)	Moderate[a]	

Influenza-like symptoms (2,101,102)	5 RCT; 10,695	44 in 1000	**142.5 more in 1000 (105.5 more to 188.4 more)**	**OR** 4.98 (3.82 to 6.58)‡	Moderate[a]	
Arthritis and arthralgia (2,101,102)	6 RCT; 11,171	145 in 1000	**178.5 more in 1000 (137.4 more to 224.1 more)**	**OR** 2.82 (2.32 to 3.45)‡	Moderate[a]	
Myalgia (2,101,102)	5 RCT; 11,065	17 in 1000	**70.7 more in 1000 (54.6 more to 90.8 more)**	**OR** 5.56 (4.46 to 6.99)‡	Moderate[a]	
Arthralgia, myalgia, pyrexia, chills, & influenza-like symptoms (2,101,102)	6 RCT; 11,676	219 in 1000	**422.8 more in 1000 (398.6 more to 446.3 more)**	**OR** 6.39 (5.76 to 7.09)‡	Low[a,c]	**May increase**
Chills (104)	2 RCT; 799	12 in 1000	**33.7 more in 1000 (3.0 more to 127.2 more)**	3.81 (1.25 to 11.6)	Low[a,b,d]	
Non-serious GI AE (2,101,102)	3 RCT; 840	79 in 1000	30.9 more in 1000 (11.8 fewer to 97.6 more)	**OR** 1.44 (0.84 to 2.50)‡	Low[a,b,d]	**May not increase**
Very uncertain: discontinuation due to AE[a,b,d] (5,100).						

AE=adverse event; GI=gastrointestinal; NR=not reported; NS=not statistically significant; RCT=randomized controlled trial;
*The control event rate is the median rate in the control group for studies in the analysis. These were extracted directly from the systematic reviews when possible. Otherwise, we extracted these data from the included primary studies when there were ≤5 in the analysis or used the 5 largest studies from larger analyses to calculate the control event rate.
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision; e=Large magnitude of effect (+1)
‡Odds ratio derived from exact logistic regression meta-analysis (101).

Table 6.4 Harms of Treatment (Bisphosphonates as a class)

- Bisphosphonates as a class may increase atypical femoral fractures (any, with long-term treatment, >3 years = 11 (7 to 14) in 10,000 in-years, subtrochanteric = 0.2-1.1 more per 1000) and osteonecrosis of the jaw (0.3-43.0 in 1000).
- Bisphosphonates probably do not increase stroke or myocardial infarction (MI) and may not increase the composite of nonfatal stroke, MI or death from vascular cause or cardiovascular mortality.
- The evidence for esophageal cancer and atrial fibrillation was very uncertain.

Outcome	Studies; sample size	Assumed pop. risk*	Absolute effects (95% CI)	Relative RR unless otherwise stated	Certainty	Judgement

				(95% CI)		
Bisphosphonate vs. placebo or no treatment						
Serious adverse events						
Atypical femoral fracture (any, with long-term treatment, >3 years) (99)	1 cohort; ~2.8 mill	0.3 in 1000[†]	**11 (7 to 14) in 10,000 in-years**	**OR** 126 (55 to 288)	Low[a,e]	**May increase**
	1 case-control; 1,368		**NA**	**OR** 93 (66 to 132) for >5 years of use		
	1 case-control; 290		**NA**	**OR** 25.65 (10.74 to 61.28)		
Atypical femoral fracture (subtrochanteric) (2,101,102)	3 RCT; NR	0.3 in 1000[†]	**1.0 more in 1000 (2.6 fewer to 41.1 more)**	1.33 (0.14 to 14.7)	Low[b]	
	1 SR of 11 observational; NR		**0.2 more in 1000 (0.1 more to 0.4 more)**	1.70 (1.22 to 2.37)		
	Pooled: safety databases; NR		**1.1 more in 1000 (0.7 more to 1.5 more)**	4.51 (3.44 to 5.92)		
Osteonecrosis of the jaw (2,101,102)	Case series, SRs; NR	NR	**Inconsistent, 0.3 to 43.0 in 1000**		Low[b]	
Stroke (105)	2 RCT; 9,825	33 in 1000	2.0 more in 1000 (5.9 fewer to 11.6 more)	1.06 (0.82 to 1.35)	Moderate[d]	**Probably does not increase**
Myocardial infarction (105)	5 RCT; 10,4040	12 in 1000	2.2 fewer in 1000 (5.2 fewer to 2.0 more)	0.82 (0.57 to 1.17)	Moderate[d]	
Nonfatal stroke, MI, death - vascular cause (105)	12 RCT; 16,888	67 in 1000	3.4 fewer in 1000 (8.7 fewer to 3.4 more)	0.95 (0.87 to 1.05)	Low[a,c]	**May not increase**
Cardiovascular mortality (105)	5 RCT; 10,165	22 in 1000	2.6 fewer in 1000 (8.4 fewer to 5.1 more)	0.88 (0.62 to 1.23)	Low[a,d]	
Very uncertain: esophageal cancer[b] (2,101,102) and atrial fibrillation[b,d] (2,101,102). No evidence: effect of long-term bisphosphonates (>3 years) on the risk of osteonecrosis of the jaw.						

MI=myocardial infarction; NA=not applicable; NR=not reported; RCT=randomized controlled trial; SR=systematic review
*The control event rate is the median rate in the control group for studies in the analysis. These were extracted directly from the systematic reviews when possible. Otherwise, we extracted these data from the included primary studies when there were ≤5 in the analysis or used the 5 largest studies from larger analyses to calculate the control event rate.

†The absolute effect (and its 95% CI) without treatment (i.e. baseline rate) is based on the estimated risk in the comparison group; the effect with treatment is based on applying the relative effect of the intervention (and its 95% CI) to the effect without treatment. When an OR is presented, we used the following formula recommended in the Cochrane manual: intervention risk per 1000 = 1000 x (OR x ACR / 1 – ACR + (OR x ACR))
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision; e=Large magnitude of effect (+1)

Table 6.5 Harms of Treatment (Denosumab)

- Denosumab may not increase any serious AE, serious cardiac events, stroke, the composite of cardiovascular death, MI or stroke or the composite of cardiovascular death, MI, stroke or heart failure.
- Denosumab probably does not increase any non-serious AE and may not increase discontinuation due to AEs.
- Evidence for serious infections, venous thromboembolism, composite of stroke, atrial fibrillation, heart failure and coronary artery disease, atrial fibrillation, atypical femoral fractures and osteonecrosis of the jaw is very uncertain
- Denosumab probably increases non-serious GI AEs (64.5 more in 1,000), rash or eczema (15.8 more in 1,000) and infections (1.8 more in 1,000) and may increase eczema (13.8 more in 1,000).
- Denosumab probably does not increase any non-serious AEs and may not increase discontinuations due to AEs.
- Evidence for arthralgia, injection-site reactions and rash was very uncertain
- Evidence for rebound fractures associated with discontinuation was very uncertain for non-vertebral, clinical vertebral and multiple clinical vertebral fractures.

Outcome	Studies; sample size	Assumed pop. risk*	Absolute effects (95% CI)	Relative RR unless otherwise stated (95% CI)	Certainty	Judgement
Denosumab vs. placebo						
Serious adverse events						
Any serious AE (5,100)	4 RCT; 8,663	81 per 1000	9.8 more per 1000 (10.0 fewer to 35.2 more)	1.12 (0.88 to 1.44)	Low[d]	**May not increase**
Serious cardiac events (2,101,102)	3 RCT; NR	NR	Cannot be calculated; NS difference	**OR** 1.04 (0.87 to 1.25)[‡]	Low[a,b,d]	
Stroke (106)	2 RCT; 7,733	NR	Cannot be calculated; NS difference	1.4% vs. 1.4%	Low[a,b,d]	
Cardiovascular death + MI +	4 RCT; 9,066	NR	Cannot be calculated; NS	1.00 (0.82 to 1.23)	Low[a,c]	

stroke (106)			difference			
Cardiovascular death + MI + stroke + heart failure (107)	4 RCT; 9,066	NR	Cannot be calculated; NS difference	0.99 (0.83 to 1.19)	Low[a,c]	
Very uncertain: serious infections[d] (5,100), venous thromboembolism[a,b,d] (108); composite of stroke, atrial fibrillation, heart failure, coronary artery disease[a,b,c,d] (106); atrial fibrillation[a,b,d] (2,101,102), atypical femoral fractures[a,b,d] (99,108), and osteonecrosis of the jaw[a,b,d] (99,108). No evidence: serious GI AE (any; GI perforations, ulcers, bleeds; serious esophageal) (2,101,102), GI cancer (2,101,102), thromboembolic events (2,101,102), cardiac death (2,101,102).						
Non-serious adverse events and discontinuation due to AE						
Non-serious GI AE (2,101,102)	3 RCT; 8,454	105 in 1000	**64.5 more in 1000 (26.4 more to 113.3 more)**	**OR** 1.74 (1.29 to 2.38)[‡]	Moderate[a]	**Probably increases**
Rash or eczema (5,100)	3 RCT; 8,454	17 in 1000	**15.8 more in 1000 (7.6 more to 27.0 more)**	**OR** 1.96 (1.46 to 2.66)[‡]	Moderate[a]	
Infections (2,101,102)	4 RCT; 8,691	7 in 1000	**1.8 more in 1000 (0.1 more to 4.0 more)**	1.26 (1.01 to 1.57)	Moderate[a]	
Eczema (5,100)	1 RCT; 7,762	17 in 1000	**13.8 more in 1000 (5.8 more to 24.5 more)**	1.81 (1.34 to 2.44)	Low[a,b]	**May increase**
Any non-serious AE (108)	5 RCT; 9,201	907 in 1000	No difference in 1000 (9.1 fewer to 9.1 more)	1.00 (0.99 to 1.01)	Moderate[a]	**Probably does not increase**
Discontinuation due to AE (5,100)	3 RCT; 8,451	21 in 1000	Cannot be calculated; NS difference	1.14 (0.85 to 1.52)	Low[a,b,d]	**May not increase**
Very uncertain: arthralgia[a,b,d] (107), injection-site reactions[a,b,d] (5,100), and rash[a,b,d] (5,100). No evidence: influenza-like symptoms.						
Rebound fractures with discontinuation (discontinuation of denosumab vs. discontinuation of placebo)						
Very uncertain: non-vertebral fractures[a,b,c,d] (107), clinical vertebral fractures[a,b,c,d] (107), and multiple clinical vertebral fractures[a,b,c,d] (107). No evidence: There was **no evidence located** to comment on the effect of discontinuing denosumab on the risk of hip fracture.						

AE=adverse event; GI=gastrointestinal; MI=myocardial infarction; NR=not reported; NS=not statistically significant; RCT=randomized controlled trial

*The control event rate is the median rate in the control group for studies in the analysis. These were extracted directly from the systematic reviews when possible. Otherwise, we extracted these data from the included primary studies when there were ≤5 in the analysis or used the 5 largest studies from larger analyses to calculate the control event rate.

		†The absolute effect (and its 95% CI) without treatment (i.e. baseline rate) is based on the estimated risk in the comparison group; the effect with treatment is based on applying the relative effect of the intervention (and its 95% CI) to the effect without treatment. When an OR is presented, we used the following formula recommended in the Cochrane manual: intervention risk per 1000 = 1000 x (OR x ACR / 1 – ACR + (OR x ACR)) a=risk of bias; b=inconsistency; c=indirectness; d=imprecision; e=Large magnitude of effect (+1) This review did not include all possible rare adverse events caused by treatment (e.g. hypocalcemia caused by denosumab). Guidelines providing recommendations for pharmaceutical treatment may discuss this in greater detail. **Overall severity of undesirable anticipated effects** The increase in adverse events was seen as small (i.e. very rare SAEs with wide confidence intervals, more common but non-serious AEs. Although level of overdiagnosis was moderate (i.e. a large portion of the screened population will be overdiagnosed) the resulting harm (anxiety, labelling) was thought to be not as severe as being overdiagnosed with cancer (i.e. does not require surgery, chemo, etc.), resulting in an overall rating of “small” for undesirable effects.	

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** **X** Very low (males ≥40 and females 40-65 years) **X** Low (females ≥65 years) ○ Moderate ○High ○No included studies	**JUDGEMENT – CERTAINTY** When considering the benefits and harms of screening for the "selected population" (offer-to-screen among females ≥65 years willing to independently complete a mailed fracture risk questionnaire), the overall certainty of the evidence for an effect of screening to prevent fragility fractures was Low. When considering the benefits and harms of screening from the general population (offer-to-screen among females ≥65 years), the overall certainty of the evidence for an effect of screening to prevent fragility fractures was Low. When considering the benefits and harms of screening for the general population (females 40-64 or males ≥65 years), the overall certainty of the evidence for an effect of screening to prevent fragility fractures was Very low. There was no evidence for males 40-64 years (Very low) This resulted in a combined rating of Females ≥65 years = Low certainty Females 40-64 years = Very low certainty Males ≥40 years = Very low certainty **SCREENING VS NO SCREENING (KQ1a)**	

Outcomes for "Selected population" (offer-to-screen among females ≥65 years willing to independently complete a mailed fracture risk questionnaire).

Outcome	Certainty
Hip fractures	Moderate
Clinical fragility fractures	Moderate
~~Fracture related mortality~~	~~No evidence (very low)~~
All-cause mortality	Moderate
~~Functionality and disability~~	~~No evidence (very low)~~
Quality of life or well-being	~~Very low to~~ moderate
Serious adverse events	~~Very low (KQ1) to~~ moderate (KQ3b)
Overdiagnosis	Low
~~Discontinuation due to adverse events~~	~~Very low to moderate (KQ3b)~~
Non-serious adverse events	Low to moderate (KQ3b)

- GRADE methods usually require that the overall rating be based on the lowest certainty outcome (109).
- An overall rating of "low certainty" was chosen despite the very-low certainty found on some outcomes. This follows the GRADE methodology where certain outcomes may cease to be considered critical if they would not change the strength or direction of the recommendation. Additionally, "If there is higher quality of evidence for some critical outcomes to support a decision, then one need not rate down quality of evidence because of lower confidence in estimates of effects on other critical outcomes that support the same recommendation" (109). Rationale for the re-classification of specific outcomes are listed below:
    - Fracture related-mortality was deemed not necessary as the higher certainty outcome of all-cause mortality did not show an effect.

- Functionality and disability, and Quality of life or well-being were considered not necessary due to the higher certainty outcome of hip fracture (which would impact these outcomes). Additionally, there was one analysis with moderate certainty that showed no effect on quality of life.
- The outcome of serious adverse events (KQ1) was not relevant as this was studied with greater detail and follow-up in treatment trials from KQ3.
- The outcome of Discontinuation due to adverse events was deemed not necessary due to the higher certainty outcome evidence from serious and non-serious adverse events.

- **The overall rating is the lowest of the remaining outcome certainties = Low**

Outcomes for All eligible (offer-to-screen among the general population) Females ≥65 years

Outcome	Certainty
Hip fractures	Low
Clinical fragility fractures	Low
~~Fracture related mortality~~	~~No evidence (very low)~~
All-cause mortality	Low
~~Functionality and disability~~	~~No evidence (very low)~~
~~Quality of life or well-being~~	~~No evidence (very low)~~
Serious adverse events	Moderate (KQ3b)
~~Overdiagnosis~~	~~No evidence (very low)~~
~~Discontinuation due to adverse events~~	~~Very low to moderate (KQ3b)~~
Non-serious adverse events	Low to moderate (KQ3b)

- GRADE methods usually require that the overall rating be based on the lowest certainty outcome (109).

- An overall rating of “low certainty” was chosen despite the very-low certainty found on some outcomes. This follows the GRADE methodology where certain outcomes may cease to be considered critical if they would not change the strength or direction of the recommendation. Additionally, “If there is higher quality of evidence for some critical outcomes to support a decision, then one need not rate down quality of evidence because of lower confidence in estimates of effects on other critical outcomes that support the same recommendation” (109). Rationale for the re-classification of specific outcomes are listed below:
    - Fracture related-mortality was deemed not necessary as the higher certainty outcome of all-cause mortality did not show an effect.
    - Functionality and disability, and Quality of life or well-being were considered not necessary due to the higher certainty outcome of hip fracture (which would impact these outcomes). Additionally, there was one analysis with moderate certainty that showed no effect on quality of life for selected populations (see above).
    - The outcome of serious adverse events (KQ1) was not relevant as this was studied with greater detail and follow-up in treatment trials from KQ3.
    - The outcome of overdiagnosis was deemed not necessary for this population due to the higher certainty outcome evidence from the “Selected population”.
    - The outcome of Discontinuation due to adverse events was deemed not necessary due to the higher certainty outcome evidence from serious and non-serious adverse events.
- **The overall rating is the lowest of the remaining outcome certainties = Low**

Outcomes for All eligible (general population) Females 40-64 years

Outcome	Certainty
Hip fractures	Very low
Clinical fragility fractures	Very low
Fracture related mortality	No evidence (very low)
All-cause mortality	Very low to Moderate
Functionality and disability	No evidence (very low)

Quality of life or well-being	Very low to Low
Serious adverse events	No evidence (very low)
Overdiagnosis	No evidence (very low)
Discontinuation due to adverse events	Very low to moderate (KQ3b)
Non-serious adverse events	Low to moderate (KQ3b)

- **The overall rating is the lowest of the outcome certainties = Very Low**

Outcomes for All eligible (general population) Males ≥65 years

Outcome	Certainty
Hip fractures	Very low
Clinical fragility fractures	No evidence (very low)
Fracture related mortality	No evidence (very low)
All-cause mortality	No evidence (very low)
Functionality and disability	No evidence (very low)
Quality of life or well-being	No evidence (very low)
Serious adverse events	Moderate (KQ3b)
Overdiagnosis	No evidence (very low)
Discontinuation due to adverse events	Very low to moderate (KQ3b)
Non-serious adverse events	Low to moderate (KQ3b)

		- **The overall rating is the lowest of the outcome certainties = Very Low** **Outcomes for All eligible (general population) Males 40-64 years** No evidence, therefore the overall rating is Very Low **This resulted in a combined overall rating of:** - **The overall certainty of the evidence for all females (selected or general population) ≥65 years = Low** - **The overall certainty of the evidence for all females 40-64 years = Very low** - **The overall certainty of the evidence for all males ≥40 years = Very low**	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** **X** Important uncertainty or variability ○Possibly important uncertainty or variability ○Probably no important uncertainty or variability	**KQ4: For patients ≥40 years, what is the acceptability (i.e., positive attitudes, intentions, willingness, uptake) of screening and/or initiating treatment to prevent fragility fractures when considering the possible benefits and harms from screening and/or treatment?** **JUDGEMENT – VALUES** **Younger (lower risk) females (age 50-65 years) have a high willingness to be screened.** **There is large heterogeneity in the level of risk at which patients may be accepting of initiating treatment, and treatment effects appear to be overestimated by the patients.** **There is low to moderate certainty in the evidence on patient acceptability of treatment indicating that a substantial proportion of people (possibly >50%) may not value the benefits as more important than the harms. The evidence is indirect to screening since most studies examined treatment decisions**	

	○No important uncertainty or variability	**Table 7.1: Patient acceptability of screening and/or initiating treatment**	

Studies; sample size	Certainty*	What does the evidence say?
Acceptance of screening		
Females 50-65 y 1 observational; 258 (110)	Low[a-d]	Females aged 50-65 years (low risk) may have a high intention to be screened, and this intention may not be changed after reading a 1-page decision support sheet (1 study, n=258) (110).
Acceptance of treatment with information		
Adults (predominantly female) ≥50 y, mean 63-72 y, 2 observational, 2 RCT; 980 (111–114)	Low[a,c]	Patients' preference for treatment vs. no treatment may be highly variable (2 studies, n=287) (111,112). After receiving information on their personal fracture risk, relatively few (19 to 39%) patients may be willing to accept treatment (2 studies, n=593) (113,114).
Acceptance of treatment with decision aids		
Postmenopausal females ≥45 y, mean 62-69 y 4 observational (5 reports); ~324 (115–119)	Moderate[a,d]	Few (5-20%) postmenopausal females with osteoporosis or osteopenia who read decisions aids and are aware of their fracture risk are willing to initiate treatment (2 studies, n~240) (115–117). Somewhat more (41-44%) may be willing to start treatment when the decision aid is used during a clinical encounter or when they have had a previous fracture or are at higher fracture risk (32-45%; 1 study, n=208) (2 studies, n=84) (118,119). Overall, a minority of postmenopausal females at increased risk for fracture may accept treatment.
Minimum acceptable benefit of treatment		
Adults ≥50 y, mean 60-72 y, 3 observational; 741 (111,112,120)	Low[a,c]	About two-thirds (64%) of adults ≥50 years may have overly optimistic views of the benefits of treatment (1 study, n=354) (120); these views may be highly variable (3 studies, n=741) (111,112,120) Patients may require a reduction of 20 to 200 fractures per 1000 to consider 10 y of bisphosphonate treatment acceptable (1 study, n=354) (120).
Level of risk at which treatment is acceptable		
Adults (predominantly female), ≥45 y, 6 observational; 1091 (111,113–115,119,121)	Low[a,c]	Among adults ≥45 years (97% female; aware of personal risk) there is large heterogeneity in the level of risk at which treatment would be considered (111,113–115,119,121). Many (19 to 51%) are willing to accept treatment at low levels of fracture risk (5 to 20%), but a large proportion (44 to 68%) of high-risk females (≥3% hip or ≥20% osteoporotic fracture risk; ≥30% in one study) would choose not to be treated (3 studies, n=378) (113,115,119).

RCT=randomized controlled trial; y=years

*When our assessment of the certainty of evidence fell between levels, we assigned the level that best represented our actual
a=risk of bias; b=inconsistency; c=indirectness; d=imprecision; e=Large magnitude of effect (+1)

BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

X Favors the comparison (males ≥40 and females 40-65 years)
○ Probably favors the comparison
○Does not favor either the intervention or the comparison
X Probably

JUDGEMENT

The balance of benefits and harms may favour the intervention for females ≥65 years
The balance of benefits and harms favours the comparison for females 40-64 and males ≥40 years

	Females ≥65 years (selected population) Overall certainty: Low	Females ≥65 years (general population) Overall certainty: Low	Females 40-64 years (general population) Overall certainty: Very Low	Males ≥65 years Overall certainty: Very Low	Males 40-64 years Overall certainty: Very Low
Population	Females ≥65 years (SCOOP, SALT and ROSE RCTs + Kern CCT for hip fractures only) (24–27)[11]	Females 68-80 years (ROSE RCT) (24)	Females 45-54 years (APOSS (Barr) RCT) (23)	Males ≥65 years (Kern CCT) (27)	No evidence
Hip fractures	**Probably reduces**	**May not reduce**	**Very uncertain**	**Very uncertain**	**No evidence**

Notes: Screening RCTs had a higher rate of hip fracture and lower rate of MOF and clinical fragility fracture than Canadian data (see footnote 11). Treatment RCTs had lower hip and MOF rates than Canadian data (see footnotes 12 -14)

The frequency of screening was not examined in this analysis, but may be a consideration for implementation

- Osteoporosis Canada recommends repeating BMD in 1–

[11] This is a population with a mean risk of hip and MOF of 3.1% and 8.4% respectively (higher for hip and lower for MOF than Canadian females (2.0% and 16.8% respectively).

	favors the intervention (females ≥65 years) ○Favors the intervention ○Varies ○Don't know		Study data: 6.2 (2.8-9.0) fewer per 1000 General population: 4.0 (1.8-5.8) fewer per 1,000 Moderate to high certainty	Study data: 0.3 fewer (4.2 fewer to 3.9 more) per 1000 General population: 0.2 fewer (2.4 fewer to 2.2 more) fewer per 1,000 Low certainty			3 years to reassess risk (4). - USPSTF states "limited evidence from 2 good-quality studies found no benefit in predicting fractures from repeating bone measurement testing 4 to 8 years after initial screening." (6)
			Indirect evidence[12]: Bisphosphonates **may reduce** 2.9 (study data) and 5.3 (general population) fewer in 1,000. Low certainty			Indirect evidence[13]: Zoledronic acid **may not reduce** Study data: 2.2 more (1.6 fewer to 42.0 more) per 1,000 General population: 16.7 more (12.9 fewer to 256.0 more) per 1,000 Low certainty	

[12] This is a population with a mean risk of hip and clinical fragility fracture of 1.1% and 5.8% respectively (lower for hip and MOF than Canadian females (2.0% and 20.2% respectively)).

[13] This is a population with a mean risk of hip of 0.4% (lower than Canadian males (3.3%)).

		Clinical fragility fractures	**Probably reduces** Study data: 5.9 (0.8-10.9) fewer per 1000 General population: 11.8 (1.7-21.8) fewer per 1,000 Moderate to high certainty	**May not reduce** Study data: 1.0 fewer (8.0 fewer to 6.0 more) per 1000 General population: 1.7 fewer (13.4 fewer to 10.1 more) per 1,000 Low certainty	**Very uncertain**	**No evidence**	**No evidence**	
			Indirect evidence[14] Bisphosphonates **probably reduces** 11.1 (study data) and 33.6 (general population) fewer in 1,000 and denosumab **probably reduces** 12.2 (study data) and 51.5 (general population) fewer in 1,000 Moderate certainty			Indirect evidence[15]**:** Zoledronic acid **may not reduce** Study data: 7.7 fewer (14.2 fewer to 9.5 more) per 1,000 General population: 42.3 fewer (81.0 fewer to 48.0 more) per 1,000 Low certainty	

[14] This is a population with a mean risk of clinical fragility fracture of 4.2% (lower than for Canadian females (20.2%)).

[15] This is a population with a mean risk of clinical fragility fracture of 1.0% (lower than Canadian males (6.3%)).

		All-cause mortality	**Probably does not reduce** No difference in 1,000 (study and general population) Moderate certainty	**May not reduce** Study data: 3.5 fewer (9.4 fewer to 3.5 more) in 1000. General population: 1.7 fewer (4.6 fewer to 1.7 more) in 1,000 Low certainty	**Very uncertain to may not reduce** Study data: 0.3 fewer (9.2 fewer to 11.6 more) per 1,000 General population: No difference (0.8 fewer to 1.1 more) in 1,000 Very low to moderate certainty	**No evidence**	**No evidence**	
		Quality of life/health related quality of life	**May be little to no difference** Low to moderate certainty	**No evidence**	**Very uncertain**	**No evidence**	**No evidence**	*Paradigmatic situations in which a strong recommendation may be warranted despite low or very*

		Overdiagnosis	SCOOP: 11.8% (using hip fracture risk) (26); SALT: 19.8% (using MOF risk) (25) Among acceptors = 24.1 (SCOOP) (26); Low certainty	**No evidence**	**No evidence**	**No evidence**	**No evidence**
		Serious adverse events	**Very uncertain** (SCOOP) (26);				
			<u>Indirect evidence</u>[16] Bisphosphonates (as a class) and alendronate **may increase rare but serious harms of subtrochanteric atypical femoral fracture and osteonecrosis of the jaw** (AFF = 0.06 to 1.1 more per 1,000) (ONJ = 0.22 to 43 more per 1,000) Low certainty				
			No direct evidence				

low confidence in effect estimates (122)

1. When low quality evidence suggests benefit in a life-threatening situation

2. When low quality evidence suggests benefit and high quality evidence suggests harm or a very high cost

3. When low quality evidence suggests equivalence of two alternatives, but high quality evidence of less harm for one of the competing alternatives

4. When high quality evidence suggests equivalence of two alternatives and low quality evidence suggests harm in one alternative

[16] Majority were older females, some older males (Alendronate)

		Non-serious adverse events	Indirect evidence[17] Alendronate and denosumab **probably increase non-serious GI adverse events** 16.3 to 64.5 more respectively per 1,000. (moderate certainty). Zoledronic acid **probably increases pyrexia, headache, influenza-like symptoms, arthritis and arthralgia, myalgia.** 422.8 more per 1,000 (low certainty) Denosumab **probably increases rash/eczema** 15.8 more per 1,000 **and infections** 1.8 more per 1,000 (moderate certainty)	*5. When high quality evidence suggests modest benefits and low/very low quality evidence suggests possibility of catastrophic harm* *Additional TF criteria:* *"When there is an absence of evidence to provide confidence that there is benefit from implementing a new prevention service or when a conclusion of possible benefit requires a high level of speculation on linkages of uncertain evidence, but there is high certainty that some patients would be harmed or scarce health care resources expended, the task force may make a strong recommendation against service implementation"* (123).

There is low certainty evidence that screening with a clinical risk assessment tool (i.e. FRAX) followed by a BMD scan (where indicated*) and re-calculation of FRAX with BMD risk, may reduce hip and clinical fragility fractures in females ≥65 years

There is low certainty evidence that screening may result in 11.8-19.8% being overdiagnosed as "at risk" and may increase rare but serious harms (i.e. osteonecrosis of the jaw, atypical femoral fractures) and probably increases non-serious adverse events (e.g. gastrointestinal (reflux, nausea), headache, influenza-like symptoms, rash)

BMD-first vs Risk assessment-first screening

- Direct evidence from a trial comparing SCORE or SOF + BMD vs BMD alone was very uncertain (29)
- SCOOP, SALT and ROSE all used risk assessment-first (FRAX+/-BMD) screening (24–26)
- FRAX without BMD may be well-calibrated to predict 10-year hip fractures and is probably well-calibrated to predict 10-year clinical fragility fractures

[17] Majority were older females, some older males (Zoledronic acid)

- FRAX with BMD may perform poorly to predict 10-year hip fractures but is probably well calibrated to predict 10-year clinical fragility fractures
- CAROC[18] may be adequately calibrated to predict category of clinical fragility fracture risk. However, no screening trial has been conducted with CAROC.

RECOMMENDATIONS

FEMALES ≥65 YEARS

In females 65 years or older, we recommend screening with the Canadian FRAX risk assessment tool (without BMD) and using the 10-year absolute risk of Major Osteoporotic Fracture to facilitate shared decision-making about the possible benefits and harms of treatment. If the patient is considering preventive treatment, we recommend refining fracture risk by adding the BMD value in FRAX. (Conditional recommendation, low certainty evidence)

Considerations for implementation

- *The frequency of screening was not specifically examined as a key question for this analysis, but may be a consideration for implementation*
  - *No RCTs of different screening intervals were found during the SR for KQ1*
  - *We did not perform a systematic review of observational studies of different screening intervals*
  - *Evidence from an environmental scan of cohort studies found that repeated BMD scans at 3-8 years did not improve fracture risk prediction (females aged ≥50 years) (147-149)*
  - *A systematic review performed by the USPSTF in 2018 found that "Some observational and modeling studies have suggested screening intervals based on age, baseline BMD, and calculated projected time to transition to osteoporosis. However, limited evidence from 2 good-quality studies found no benefit in predicting fractures from repeating bone measurement testing 4 to 8 years after initial screening."* (5)

Rationale:

- *The small benefit (reduction in hip and clinical fragility fractures) outweighs the moderate risk of overdiagnosis, small increased risk of rare serious harms (osteonecrosis of the jaw, atypical femoral fractures) and small increase in non-serious AEs (e.g. GI AEs, arthralgia, influenza-like symptoms)*

[18] CAROC is a semi-quantitative method for estimating 10-year absolute risk of a MOF in postmenopausal females and males over age 50. Three zones (low: < 10%, moderate: 10-20, high: > 20%). Based on age, BMD, sex, previous fracture after age 40 and glucocorticoid use (142).

		- *The recommendation for a risk assessment-first screening process is based on the methods used in the trials (i.e. FRAX (without BMD) followed by BMD assessment if indicated and recalculation of FRAX with BMD)*
		  o *Risk assessment-first screening limits the number of women who require BMD scans to only those at increased risk (based on FRAX results and shared decision making)*
		  o *Additionally, evidence from KQ2 showed that Canadian FRAX (without BMD) may be well-calibrated to predict 10-year hip or clinical fragility fracture*
		  o *The CAROC tool is also commonly used but was not recommended as part of the risk assessment-first screening process as it does not allow risk calculation without BMD*
		- *The trials used a threshold for access to BMD and treatment, however, the WG recommends shared decision making at each step*
		- *This recommendation is conditional based on the low certainty of the evidence, differences in benefit seen in "select" vs general populations and the variable patient values and preferences*
		
		<u>FEMALES 40-65 YEARS</u>
		In females 40-64 years, we recommend not screening. (Strong recommendation, very low certainty evidence)
		
		Rationale:
		- *The evidence about all eligible / offer-to-screen populations (females 45-54 years) is very uncertain.*
		- *It is uncertain whether females 40-64 years would benefit from screening. However, there is high certainty that some patients may be harmed (e.g. overdiagnosis) and costs would increase*
		
		• *This recommendation follows the TF criteria for making a strong recommendation based on very low certainty evidence:*
		  – *"When there is an absence of evidence to provide confidence that there is benefit from implementing a new prevention service or when a conclusion of possible benefit requires a high level of speculation on linkages of uncertain evidence, but there is high certainty that some patients would be harmed or scarce health care resources expended, the task force may make a strong recommendation against service implementation" (see notes)*
		
		<u>MALES ≥40 YEARS</u>
		In males ≥40 years we recommend not screening. (Strong recommendation, very low certainty evidence)
		
		Rationale:	

		- *The evidence about offer-to-screen in selected populations (males ≥65 years) is very uncertain.* - *There was no evidence for males 40-64 years* - *It is uncertain whether males ≥40 would benefit from screening. However, there is high certainty that some patients may be harmed (e.g. overdiagnosis) and costs would increase* • *This recommendation follows the TF criteria for making a strong recommendation based on very low certainty evidence:* – *"When there is an absence of evidence to provide confidence that there is benefit from implementing a new prevention service or when a conclusion of possible benefit requires a high level of speculation on linkages of uncertain evidence, but there is high certainty that some patients would be harmed or scarce health care resources expended, the task force may make a strong recommendation against service implementation" (see notes)*	

.RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○Large costs ○Moderate costs ○Negligible costs and savings **X** Moderate savings ○Large savings ○Varies ○Don't know	A systematic cost-effectiveness analysis was not conducted as part of the systematic review. **JUDGEMENT – RESOURCES REQUIRED** **There would be moderate cost savings with a strong recommendation against screening for men and younger females. Canadian data (2009) indicates that 35% of females 40-64 years and 10% of males ≥40 years (20% of males ≥65 years) self-reported receiving BMD scans** (140)**. Additionally, there should be savings if the Task Force recommends for risk assessment-first screening among females ≥65 years (e.g. some BMD scans could be avoided based on FRAX score and shared decision making).** **There may be additional costs if recommending for screening females ≥65 years as Canadian self-reported data (2009) found that 32% of females in this age group had never received a BMD test** (140)**. However, as a conditional recommendation this would depend on the results of shared decision making.** **A cost-effectiveness analysis of the SCOOP trial (5 year follow-up) showed that screening prevented fractures at a cost of £4,478 and £7,694 per fracture for MOF and hip fractures, respectively. It also improved QALY at an average incremental cost of £2,772 (124).** **A Markov model of the SCOOP trial estimated long-term (mean=14 year) outcomes for screened vs unscreened individuals. Screening of 1,000 patients saved 9 hip fractures and 20 non-hip fractures. The screening arm also saved £286 in comparison with usual management arm (125).**	Estimated cost for BMD (DEXA) in Ontario (126): (Billing schedule) $47.75 for one site $61.55 for two sites (hip and spine) Associated costs - Radiation technologist - Radiologist - Family doctor - Medication There may be significant patient costs of medication as some provincial drug coverage only provides restricted access to certain medications (e.g. denosumab, zoledronic acid). Canada >=65 years medication coverage (127,128) Alendronate (CAD$122-$182/ year) or Risedronate (CAD$130-$600 /year): Coverage varies by province (open access or restricted access) Zoledronic acid (CAD$335/year):

COST-EFFECTIVENESS ANALYSES OF THE SCOOP STUDY:

2. Turner DA, Khioe RFS, Shepstone L, Lenaghan E, Cooper C, Gittoes N, et al. The Cost-Effectiveness of Screening in the Community to Reduce Osteoporotic Fractures in Older Women in the UK: Economic Evaluation of the SCOOP Study. J Bone Miner Res 2018 May;33(5):845-851. (124)

Perspective: A "within trial" economic analysis was undertaken on an "intention-to-treat" basis from the perspective of a national health payer, the UK National Health Service (NHS).

Methods: **Five-year time horizon** for cost (2013/14) per quality adjusted life year (QALY), osteoporosis-related fracture prevented (hip, vertebral, wrist), and hip fracture prevented. Point estimates from RCT for hip and osteoporotic fractures used. QALYs estimated (from AUC) from EQ-5D scores across all data points (at baseline, 6, 12 and annually; major imputation requited for 36% participants); tariffs from UK population from 10-year duration TTOs. Screening resources (BMD/DXA scans, calculation and clinical review of fracture risk, GP consultation; identifying women) were recorded as part of the SCOOP study and costed per study data or using NHS Reference costs 2013 to 2014 or unit costs of health and social care 2014. Resources and costs associated with fracture-related health care contacts (inpatient [elective or non-elective]; length of stay; short stays; and excess bed days), outpatient [by specialty & first or follow-up appointments & procedure costs], and accident and emergency (A&E) datasets using Health Resource Group codes were linked to NHS reference costs. Medication data were available for anti-osteoporosis medicines for the full period of follow-up for all study participants and were costed using prices from the British National Formulary. Sensitivity analysis using complete case analysis with patients completing all EQ5D data.

Summary: The screening arm had an average incremental **QALY gain of 0.0237** (95% CI -0.0034 to 0.00508) for the 5-year follow-up. The **cost per QALY gained was £2,772**. Cost-effectiveness acceptability curves indicated a 93% probability of the intervention being cost-effective at a threshold cost/QALY of ≤£20,000. The intervention arm prevented fractures at a cost of **£4,478 and £7,694 per fracture for osteoporosis-related hip fractures**, respectively. Complete case analysis had 2-3 times higher cost/QALYs (ICERs).

Table 8.1 Cost-effectiveness results for cases vs controls in SCOOP (130)

	Usual management	Screening
Mean costs, per patient (£)		
Inpatient	531	482
A & E	162	160

Coverage varies by province (restricted access or no coverage)
Denosumab (CAD$716/year) (restricted access in all provinces) (127,128)

In Ontario, the total cost of treatment for all hip fractures occurring in 2015/16 (in adults aged 66+) was estimated to be $255,773,130 based on direct utilization costs for the episode of care. The median cost per single episode of care was $25,015 for direct utilization costs (129).

Utilization of BMD varies by sex with 8.15% of females vs 4.81% of males aged 40+ reporting a BMD scan in 2015 (10).

22.9% of eligible adults (aged 68-70) in Ontario reported

Outpatient	191	201	
Medicines	8	13	
Non-SCOOP DXA	9	9	
Cost of SCOOP interventions	-	104	
Total costs	900	968	

2. Söreskog E, Borgström F, Shepstone L, Clarke S, Cooper C, Harvey I, et al. Long-term cost-effectiveness of screening for fracture risk in a UK primary care setting: the SCOOP study. Osteoporos Int 2020 Aug;31(8):1499-1506. (125)
Perspective: Cost-effectiveness based on the NICE's willingness-to-pay (WTP) threshold for recommending new treatment of £20,000–30,000 per QALY gained
Methods: Health economic Markov model (6-month cycles and 8 health states: wrist fracture, vertebral fracture, hip fracture, other osteoporotic fracture, post-vertebral fracture, post-hip fracture, dead and well [i.e. without fracture]; transition probabilities NR but cited studies) following a cohort from study participation until death or an age of 100 years (**mean 14 year time horizon**). Outcomes were cost per quality adjusted life year (QALY) and life year. Point estimates from RCT for various discrete fractures used (risk reductions at 5 years were used without any assumptions of longer term effects). Resource use and costs for drugs, administration, screening intervention as per above analysis from SCOOP RCT. Clinical costs (hospitalizations, nursing homes, outpatient) in the first and subsequent years after fracture were derived from two retrospective cohort studies that estimated fracture costs in postmenopausal females in the UK. Quality of life weights for each health state, in the first year after fracture and subsequent years (for hip and vertebral), respectively, were derived from the International Costs and Utilities Related to Osteoporotic fractures Study (ICUROS). Annual mortality in the general female population was obtained from the Office for National Statistics dataset. The relative risks of death in patients who had sustained a fracture compared with the general population were derived from a study by Jönsson et al. In agreement with previous health economic studies of osteoporotic treatments it was assumed that 30% of the excess mortality after a hip, vertebral, wrist and other osteoporotic fracture was related to the fracture event. Probabilistic and deterministic sensitivity analyses including if no effect on non-hip fractures and age.
Summary: Screening of 1000 patients saved 9 hip fractures and 20 non-hip fractures over the remaining lifetime (mean 14 years) compared with usual management. Per patient, the screening arm **saved £286 and gained 0.015 QALYs and 0.002 life years in comparison with the usual management arm. 97% probability of cost-effective at**

ever being screened in 2017/18 (129).

13.4% of BMD scans in Ontario were performed on "low risk" adults aged ≥40 years in 2017/18 (129).

WTP £20,000 and 98% at £30,000; cost-saving in 87% of simulations. Deterministic analyses all indicated cost-savings, except for at age 71 where screening became cost-neutral.

Table 8.2 Long-term cost-effectiveness results (Markov model) (125)

	Usual management	Screening	Screening vs. usual management
Mean costs, per patient (£)			
Hospitalisations	3059	2934	− 125
Nursing home	6056	5645	− 410
Outpatient	378	363	− 15
Total morbidity cost	9493	8942	− 551
Drugs	12	43	31
Treatment management	92	326	234
Total intervention cost	104	369	265
Total cost	**9596**	**9310**	**−286**

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low **X** Low ○ Moderate ○High ○No included studies	A systematic cost-effectiveness analysis was not conducted as part of the systematic review. **JUDGEMENT – CERTAINTY OF EVIDENCE OF RESOURCE REQUIREMENTS** **There are serious limitations due to indirectness and risk of bias with the Turner et al., 2018 study.** **There are serious concerns due to indirectness and some concerns with risk of bias with the Soreskog et al., 2020 study.** **Overall for selected population, there is low certainty for being highly cost-effective (ICERs low) or cost-saving to the healthcare system (indirectness and risk of bias), but moderate certainty for likely meeting typical cost-effectiveness thresholds.** 2. The Cost-Effectiveness of Screening in the Community to Reduce Osteoporotic Fractures in Older Females in the UK: Economic Evaluation of the SCOOP Study (124) Limitations: • No sensitivity for uncertainty in hip fracture reductions (e.g. 95% CI) or lack of any effect on other fractures • Large amount of missing EQ5D data. Missing cases had statistically significantly lower baseline EQ-5D, more incident fractures and higher fracture related healthcare costs. More missing EQ5D data possible for worse cases if fractured during data collection. Data collected q 6-12 months so acute changes from fractures not captured. Complete case analysis had 2-3 times higher cost/QALYs. • Short time horizon and lack of effects from fractures on longer term and/or more reductions in fractures that may occur • Estimates may be conservative from healthier sample (50% fewer deaths, more educated, higher SES) and some costs related to RCT (£44/enrolled for identifying pts)	Note: The cost-effectiveness threshold suggested by CADTH is $50,000 (130).

		• No patient or societal costs (e.g. family carers) accounted for (if desiring societal perspective). • Not costed for routine primary care contacts (e.g. for monitoring patients on meds or treating AEs) or admissions to nursing homes (may underestimate savings from fewer fractures; # admissions NR in publications) Serious indirectness: Use of all vertebral fractures, but little effect in this study. Recruitment methods and education of GPs not typical but effect on the outcomes is unclear. Short-term time horizon. Does not account for possible larger reduction in non-hip fractures seen in other RCTs and our meta-analysis (which may improve cost-effectiveness). Serious ROB from large missing data for utilities (for ICER on QALYs), not full spectrum of costs accounted for, and contamination of control groups possibly impacting risk reductions. Note: Indirect to use of clinical FRAX only (number treated may differ) or using FRAX+BMD treatment thresholds that are not age dependent. 2. Söreskog E, Borgström F, Shepstone L, Clarke S, Cooper C, Harvey I, et al. Long-term cost-effectiveness of screening for fracture risk in a UK primary care setting: the SCOOP study. Osteoporos Int 2020 Aug;31(8):1499-1506. (125) Limitations: • QALYs using age and gender matched general UK population despite outcome data in a different population. Assuming one consistent utility score for all non-fractured states and minimum 6-month period for fracture states (some utilities may change before this). • Quality of data used for transition probabilities unknown (“valid model”). • No sensitivity for uncertainty in hip fracture reductions. • Not costed for routine primary care contacts (e.g. for monitoring patients on meds or treating AEs) • No patient or societal costs (e.g. family carers) accounted for. Serious indirectness: Indirect sources for utilities and transitions. Indirect from use of all vertebral fractures, but effects minimal. Recruitment methods and education of GPs not typical but effect on the outcomes is unclear. Does not account for possible larger reduction in non-hip fractures seen in other RCTs and our meta-analysis (which may improve cost-effectiveness).	

		Some concern about ROB: from not full spectrum of costs accounted for, and contamination of control groups possibly impacting risk reductions. Studies quite consistent, but overlap in data so not too surprising. **Overall for selected population, would rate at low certainty for being highly cost-effective (ICERs low) or cost-saving to the healthcare system (indirectness and risk of bias), but moderate for likely meeting typical CE thresholds.** Please see Cost-effectiveness analysis section for the full assessment	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○Favors the comparison ○Probably favors the comparison ○Does not favor either the intervention or the comparison **X** Probably	**JUDGEMENT – COST-EFFECTIVENESS** **Based on the two studies of SCOOP, it appears to favour screening to prevent fragility fractures (cost-saving to the health-care system). However, the certainty for this conclusion is low and is based only on one RCT.** **When considering whether the cost to the healthcare system would meet typical cost-effectiveness thresholds the certainty was moderate.**	

	favors the intervention ○Favors the intervention ○Varies ○No included studies		

EQUITY	**What would be the impact on health equity?** ○Reduced ○Probably reduced ○Probably no impact **X** Probably increased ○Increased ○ Varies ○ Don't know	**JUDGEMENT – EQUITY** **A recommendation for risk assessment-first screening (females ≥65 years) may increase equity where access to BMD is limited. Risk assessment tools may help by removing unnecessary BMD for individuals at lower risk and increasing availability to those at the highest risk. However, it may decrease equity if the risk assessment tool is not calibrated for particular ethnic groups in Canada (133).** **A recommendation against screening males (≥40 years) may increase equity, where access to BMD is limited, by removing those without multiple risk factors from BMD.** **A recommendation against screening females (40-64 years) may increase equity where access to BMD is limited, by removing unnecessary BMD for individuals at lower risk.** **There are issues of equity among racialized communities, those with lower SES or those in rural/remote regions that would remain unchanged (133,135).** Significant inequities in access to BMD testing in Ontario have been described by Cadarette et al., (2007) due to age, health beliefs, education, income, use of preventive health services, region (rural/remote), and provider sex (131). Data from adults 50+ in Ontario (2017/2018) showed a 2-fold variation between the region with the highest age standardized rate of screening (10.0 per 100 in the Central[19] LHIN) and that with the lowest rate (4.2	

[19] Northern Toronto, Etobicoke, York and South Simcoe regions

per 100 in the North-West[20] LHIN) (129). Data from Manitoba (2007) also found that females in the highest SES category had significantly higher BMD utilization rates regardless of age or morbidity (132). Concerns about equitable access to BMD were identified among Indigenous populations in Canada. Leslie et al., 2012 found that they were "one half to one tenth as likely to receive post-fracture BMD testing, osteoporosis treatment, or an osteoporosis diagnosis than the general population" (133–135).

The risk of fracture varies across Canada. Age-standardized annual hip fracture rates were lowest in Quebec (124.7 per 100,000) and highest in the Northwest Territories (188.3 per 100,000) (136). Access to a family doctor in Canada also varies by province. In 2013, 15% of Canadians reported having no regular family physician (range from 7.2% in NB to 24.6% in Quebec) (137). Figure 1 provides information on the variation in between provinces in terms of fragility fractures.

Figure 1: Canadian Fragility Fracture score-card (138)

Title	Description	Score Criteria			CAN	BC	AB	SK	ON	QC
Burden of Disease										
Hip fracture risk	The age-standardized incidence of hip fracture in women	<300/100,000	300-400/100,000	>400/100,000						
Fracture risk	All osteoporotic fractures in men and women (≥50 yrs)	<15/1,000	15-20/1,000	>20/1,000						
Fracture projections	Increase in fracture number 2015-2030 (≥50 yrs)	0-25%	26-33%	>33%						
Policy Framework										
Quality of data	Data on hip fracture rates	Established hip fracture registries	Good quality hip fracture rates	Poor quality hip fracture rates						
Healthcare priority	The presence of a government-backed healthcare priority	Health priority and its implementation	Health priority but little or no implementation	Not a health priority						
Care pathway	Management in primary care	OP mainly managed in primary care	OP mainly managed by a single specialty	OP mainly managed by multiple specialties						

[20] Thunder Bay, Kenora, Rainy River and Northern regions

			
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○No ○Probably no ○ Probably yes ○Yes **X** Varies ○Don't know		

JUDGEMENT – ACCEPTABILITY

A recommendation for risk assessment-first screening (females ≥65 years) may or may not be acceptable to primary care physicians depending on current practice. Physicians may not be routinely using a risk assessment tool first, but this should be acceptable in the context of shared-decision making. The additional burden of time (to perform the initial FRAX) should be offset by a reduction in BMD scan referrals.

This recommendation may or may not be acceptable to patients depending on their willingness to accept the accuracy of a risk assessment result without BMD. However, this is currently being used in many European countries (24–26).

A recommendation against screening (males ≥40 years) may or may not be acceptable. The current Osteoporosis Canada guideline (4) recommends screening males ≥65 years but data from the 2009 CCHS showed that only 20% of this group self-reported ever being screened (140)**.**

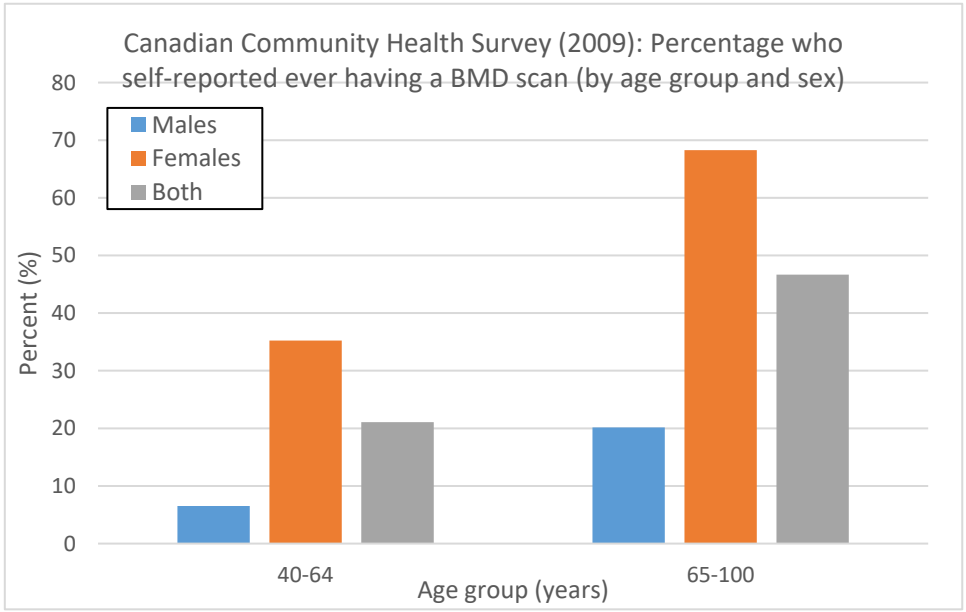
A recommendation against screening (females 40-64 years) may be acceptable. This aligns with the Osteoporosis Canada guidelines (4), but 35% of females 40-64 years reported being screened in a 2009 Canadian survey (140)**. Additionally data from KQ4 showed that females aged 50-65 had a high willingness to be screened.**

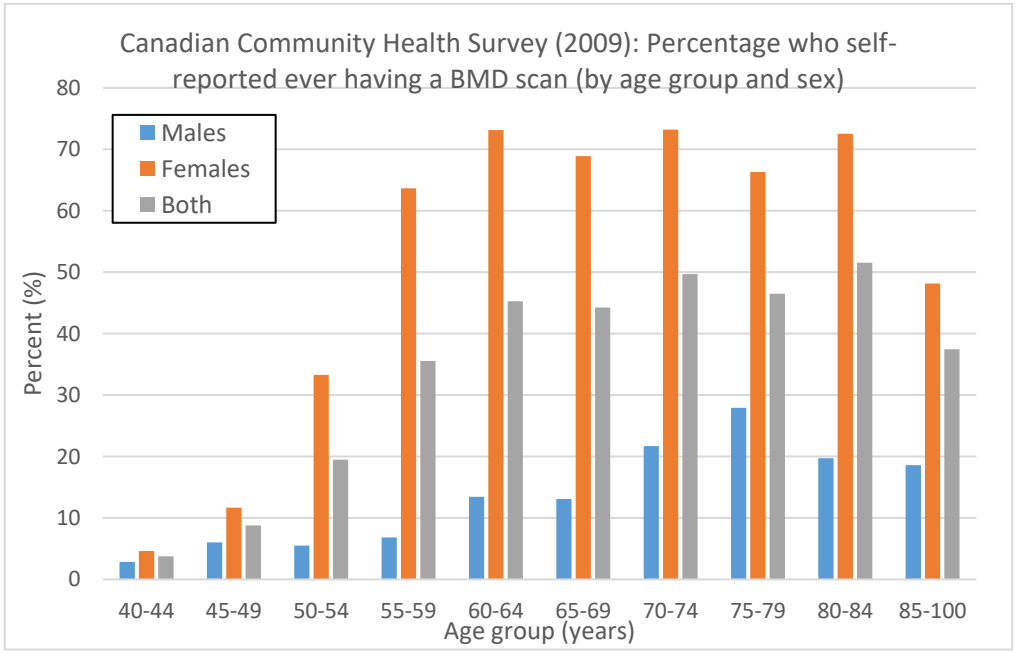
Data on whether Canadian physicians commonly use a BMD-first or risk assessment-first approach to screening is limited. However, it appears that risk assessment tools (e.g. FRAX) are more commonly recommended for use when considering treatment (i.e. following BMD assessment) (145). Screening with BMD-first to prevent fragility fractures is also currently recommended by Osteoporosis Canada for males and females ≥65 years (4).

There also appears to be a lack of clarity around when to initiate screening. A 2016 study of Ontario family physicians found "a tendency for baseline BMD testing in healthy, postmenopausal women and a lack of clarity on the appropriate age for screening for men in particular." (139)

Data from KQ4 showed that females (age 50-65 years) have a high willingness to be screened with BMD but the acceptability of risk assessment tools as part of screening is unknown. Males are less likely to screen for risk of fracture than females and therefore a recommendation against screening males may be more acceptable. In 2015, 4.81% of males and 8.15% of females over 40 years reported receiving a BMD screening test (10).

The Canadian Community Health survey (2009) collected data on the percentage of individuals who self-reported ever having a BMD scan (by age group and sex). It showed that 7% of males and 35% of females aged 40-64 reported at least one previous BMD scan. For males and females 65-100 years this number was 20% and 68% respectively (140).





Data source: Canadian Community Health Survey, 2009 at Statistics Canada (145). Analysis by: Centre for Surveillance and Applied Research, Public Health Agency of Canada.

FEASIBILITY	**Is the intervention feasible to implement?** ○No ○Probably no ○ Probably yes **X** Yes ○Varies ○Don't know	**JUDGEMENT – FEASIBILITY** **Primary care physicians** **A recommendation for risk assessment-first screening (≥65 years) should be feasible in the context of patient-centred care.** **A recommendation against screening males (≥40 years) would be feasible.** **A recommendation against screening females (40-64 years) would be feasible.**	E.g. Ontario: OHIP covers annual BMD tests for individuals at high risk for osteoporosis and future fractures. Individuals at low risk are eligible for a baseline BMD test and a second BMD test 36 months after the baseline. Third and subsequent BMD tests for low-risk individuals are insured by OHIP once every 60 months (141).

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small (Females ≥65 years)**	Moderate	Large		Varies	**Don't know (Males ≥40 and females 40-64 years)**	Trivial (general population) Small (Selected population)
UNDESIRABLE EFFECTS	Large	**Small**	Moderate	Trivial		Varies	Don't know	Small = Adverse events Moderate= Overdiagnosis
CERTAINTY OF EVIDENCE	**Very low (Males ≥40 and females 40-64 years)**	**Low (Females ≥65 years)**	Moderate	High			No included studies	(See section on Strong recommendations based on low or very low certainty evidence)
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				Screening is acceptable to patients but not necessarily treatment

	JUDGEMENT							IMPLICATIONS
BALANCE OF EFFECTS	**Favors the comparison** **(Males ≥40 and females 40-64 years)**	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention** **(Females ≥65 years)**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	Certainty that it is cost-effective (cost savings)
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know	

Appendix 10, as supplied by the authors. Appendix to: Thériault G, Limburg H, Klarenbach S, et al. Recommendations on screening for primary prevention of fragility fractures. *CMAJ* 2023. doi: 10.1503/cmaj.221219.

	JUDGEMENT							IMPLICATIONS
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	Implications for KT
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should we screen patients to prevent fragility fractures?

TYPE OF RECOMMENDATION	**Strong recommendation against the intervention** **X (Males ≥40 years and females 40-65 years)**	Conditional recommendation against the intervention o	Conditional recommendation for either the intervention or the comparison o	**Conditional recommendation for the intervention** **X (Females ≥65 years)**	Strong recommendation for the intervention o
RECOMMENDATION	**FEMALES ≥65 YEARS** In females 65 years or older, we recommend screening with the Canadian FRAX risk assessment tool (without BMD) and using the 10-year absolute risk of Major Osteoporotic Fracture to facilitate shared decision-making about the possible benefits and harms of treatment. If the patient is considering preventive treatment, we recommend refining fracture risk by adding the BMD value in FRAX.				

	(Conditional recommendation, low certainty evidence) **<u>FEMALES 40-64 YEARS</u>** In females 40-64 years, we recommend not screening. *(Strong recommendation, very low certainty evidence)* **<u>MALES ≥40 YEARS</u>** In males ≥40 years we recommend not screening. *(Strong recommendation, very low certainty evidence)* *These recommendations apply to community-dwelling individuals who are not currently on pharmacotherapy to prevent fragility fractures.*
JUSTIFICATION	Females ≥65 years - The small benefit (reduction in hip fractures and clinical fragility fractures) outweighs the moderate risk of overdiagnosis, small increased risk of rare harms (osteonecrosis of the jaw, atypical femoral fractures) and small to moderate increase in some non-serious AEs (e.g. GI AEs, arthralgia, myalgia, pyrexia, chills, & influenza-like symptoms) - Recommendation for a risk assessment-first screening process is based on the methods used in the trials (i.e. risk assessment-first screening with various European FRAX followed by BMD if indicated and evidence from KQ2 showing Canadian FRAX to probably be well-calibrated to predict 5 or 10-year hip or clinical fragility fracture. - There are also potential resource savings associated with a risk assessment-first screening process CAROC was not recommended as part of the risk assessment-first screening process as it does not allow risk calculation without BMD. Females 40-64 years - The evidence about all eligible / offer-to-screen populations (females 45-54 years) is very uncertain. - Screening females 40-64 would result in increased costs for uncertain benefits

	A conclusion of possible benefit requires a high level of speculation on linkages of uncertain evidence, but there is high certainty that some patients would be harmed or scarce health care resources expended (123). Males ≥40 years - The evidence about offer-to-screen in selected populations (males ≥65 years) is very uncertain. - There was no evidence for males 40-64 years - Screening males ≥65 years would result in Increased costs for uncertain benefits A conclusion of possible benefit requires a high level of speculation on linkages of uncertain evidence, but there is high certainty that some patients would be harmed or scarce health care resources expended (123).
SUBGROUP CONSIDERATIONS	A priori subgroups of interest included age, sex, and menopausal status. The data was stratified by age and sex with separate recommendations for females aged ≥65 years, females aged 40-64 years and males ≥40 years (see above). The evidence for males was also stratified by age with very low certainty data on males ≥65 years and no available data for males 40-64 years. As both age groups showed very uncertain results we combined them into one age category. Data specific to menopausal status was not available and a subgroup analysis was not completed for this group.
IMPLEMENTATION CONSIDERATIONS	• Ethnicity o Data underpinning the Canadian FRAX may be sparse for certain ethnicities (e.g., black, Asian, Hispanic). Country-specific versions of FRAX are available (https://frax.shef.ac.uk/FRAX/) as well as adjustments for Black, Hispanic and Asian populations in the United States FRAX; however, there have been some concerns raised about the use of race- or ethnicity-based algorithms.

	• Risk assessment-first screening
	  ○ Implementation considerations include a transition to risk assessment-first screening where this is not currently performed (e.g. direct to BMD screening)
	  ▪ Risk assessment-first screening should be acceptable in the context of shared-decision making. The additional burden of time (to perform the initial FRAX) should be offset by a reduction in BMD scan referrals.
	  ○ Additionally, CAROC is used in some jurisdictions (instead of FRAX).
	  ▪ Although CAROC may be adequately calibrated to predict category of clinical fragility fracture risk it cannot be used without BMD. Therefore, FRAX should be used as the initial risk assessment tool.
	
	• Shared decision making between the physician and patient is extremely important due to the conditional recommendation and the variable patient values and preferences
	  ○ This recommendation is conditional based on the low certainty of the evidence, differences in benefit seen in "select" vs general populations and the variable patient values and preferences
	  ○ Patients should be informed of the consequences of screening (overdiagnosis, treatment AEs) and their willingness to undergo treatment should be considered as part of the criteria for FRAX with BMD.
	
	• The frequency of screening was not specifically examined as a key question for this analysis, but may be a consideration for implementation
	  ○ No RCTs of different screening intervals were found during the SR for KQ1
	  ○ We did not perform a systematic review of observational studies of different screening intervals
	  ○ Evidence from an environmental scan of cohort studies found that repeated BMD scans at 3-8 years did not improve fracture risk prediction (females aged ≥50 years) (147-149)

	○ A systematic review performed by the USPSTF in 2018 found that "Some observational and modeling studies have suggested screening intervals based on age, baseline BMD, and calculated projected time to transition to osteoporosis. However, limited evidence from 2 good-quality studies found no benefit in predicting fractures from repeating bone measurement testing 4 to 8 years after initial screening."(5)
MONITORING AND EVALUATION	Evaluation of clinician uptake of a risk assessment-first screening program (i.e. initial screening with FRAX) will help determine uptake of the guideline. Rates of screening among the target population (females ≥65 years) should be monitored to ensure adherence to the guideline. Monitoring to ensure males and younger females are not being screened will help evaluate if the guideline is being followed.
RESEARCH PRIORITIES	There is a lack of trials on younger females (<65 years) or males (any age) for screening to reduce fragility fractures. Additionally, there is a need for evidence on the frequency of screening (i.e. screening intervals) and at what age to stop screening. Researchers are also encouraged to include a general population approach which doesn't limit the sample to only those who agree to complete a risk assessment tool. Due to the important uncertainty and variability in patient values and preferences for treatment to prevent fragility fractures, more research into this area is needed. Specifically, decision aids or other knowledge translation tools are needed to help patients understand the true benefits and harms of screening and treatment.

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Appendix 10, as supplied by the authors. Appendix to: Thériault G, Limburg H, Klarenbach S, et al. Recommendations on screening for primary prevention of fragility fractures. *CMAJ* 2023. doi: 10.1503/cmaj.221219.

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