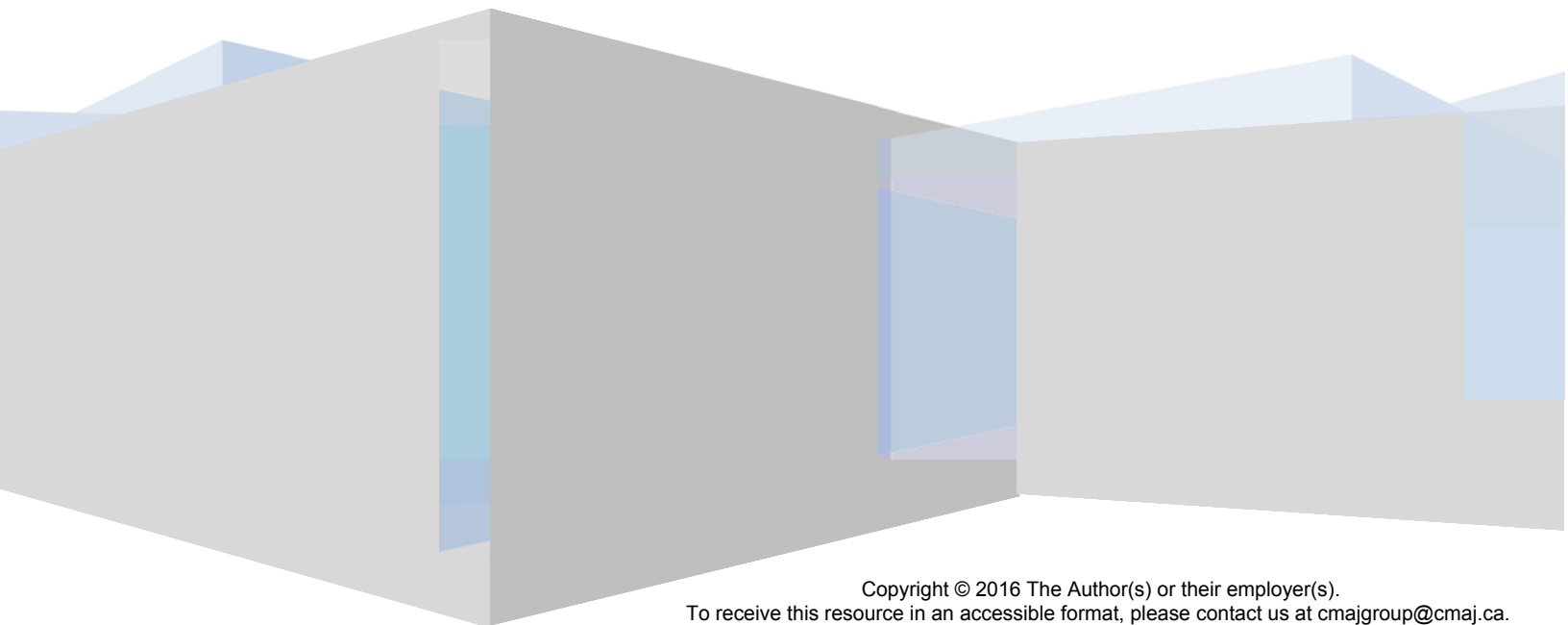


APPENDIX 1:

Fracture Prevention Recommendations for Long-Term Care

**Supplementary Materials
(as submitted by the authors)**



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Development of the Recommendations

A1. Methods

The methods to develop fracture prevention recommendations for LTC followed the Grading of Recommendations Assessment, Evaluation and Development (GRADE) approach to guideline development (Guyatt 2011; Guyatt 2008) (www.gradeworkinggroup.org).

Recommendation Panel -The panel was comprised of health providers and researchers from across Canada and included over 40 stakeholders. The panel included representatives from resident and family councils, specialists in osteoporosis care, geriatrics, and long term care organizations including the Ontario College of Family Physicians, Long-term Care Medical Directors Association of Canada, Ontario Long Term Care Physicians, Ontario Long Term Care Association, administrators, allied health professionals including the Registered Nurses' Association of Ontario, The Nurse Practitioner's Association of Ontario, librarian, Grade methodologists and epidemiologists. See A2. page 6 for participants and organizations represented. A selected smaller group, the Investigator Group (IG) of 12 members, and the Methods Group (MG) provided expert clinical guidance and support throughout the process.

Formulating questions and determining outcomes- From February to April 2012, the Investigator Group and panel were surveyed to prioritize questions on which to base the recommendations. The panel and investigator group were also surveyed to identify important outcomes to consider when making the recommendations. In addition to fractures (hip, pelvic, vertebral and non-vertebral fractures), the group identified pain, quality of life, loss of activities of daily living and mobility, mortality and adverse events which require medical attention as important outcomes. These outcomes reflect the preferences of this elderly population and their families.

Synthesis of the evidence and preparation of evidence profiles- The methods group searched for, synthesized, analyzed and presented evidence for benefits and harms, patient values and preferences, and resources. The methods group searched for systematic reviews and economic analyses, and randomized controlled trials to update these reviews, in The Cochrane Library up to June 2013; the methods group also searched reference lists for additional information about baseline risks.

The GRADE methodologist assessed the quality of evidence using the GRADE approach and presented the evidence and its quality in GRADE evidence profiles (see A4, A5, A6, A7, A8). The evidence was presented in absolute effects by applying the relative effects of treatments to baseline risks which were agreed upon by the investigator group (see A 3). Absolute effects and 95% confidence intervals around that effect were presented as "X fewer outcomes per 1000 (from X to X fewer)". The quality of the evidence or confidence in the effect estimates was assessed as high, moderate, low or very low according to the GRADE criteria (Guyatt 2008). These evidence profiles include a summary of the evidence regarding benefits and harms, the quality of the evidence, relevant resident values and preferences, resource use and feasibility issues.

Development of the Recommendations - On 11 January 2013, over 40 members of the guideline panel met to discuss the recommendations. Members of the methods group presented each GRADE evidence profile and Evidence to Recommendation Table. The panel finalised and approved the recommendations in June 2013.

The recommendations are assessed as ‘strong’ or ‘conditional’ (see Table 1). Strong recommendations are worded as ‘we recommend’ and conditional recommendations as ‘we suggest’.

TABLE 1. Interpretation of strong and conditional recommendations

Implications	Strong recommendation “we recommend...”	Conditional recommendation “we suggest...”
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals make decisions consistent with their values and preferences.

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A2. Participants and Organizations represented in the Panel

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Dr. JD. Adachi	McMaster University
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Dr. Richard Crilly	University of Western Ontario
Linda Dacres	Nurse Practitioners' Association of Ontario (NPAO)
Dr. Sid Feldman	Ontario Long Term Care Physicians (OLTCP)/OCFP (Ontario College of Family Physicians)
Dr. Chris Frank	Ontario College of Family Physicians/Canadian Geriatrics Society/ Queens University / Ontario College of Family Physicians / Canadian Geriatrics Society
Dr. Lora Giangregorio	University of Waterloo
Kerry Grady	Osteoporosis Canada
Carol Holmes	Registered Nurses' Association of Ontario (RNAO)
Dr. Rob Hopkins	McMaster University
Ina Isle	Canadian Osteoporosis Patient Network (COPN)
Dr. George Ioannidis	McMaster University
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Dr. Robert Josse	University of Toronto
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Dr. Janet Pritchard	McMaster University
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A3. Estimates of Baseline Risks in Frail Elderly

	Baseline risk	References and Notes
Overall risk of hip fracture	20/1000	Crilly 2010 (75+ years, institution and community settings); Sawka 2010 (review, institution setting)
High risk of hip fracture	60/1000	Khatib 2014 (submitted); increased relative risk of 3.0 in people with previous risk fracture compared to overall risk = 3 X 20/1000 = 60/1000)
Overall risk of vertebral fracture	20/1000	Kanis 2004 (80+ years, community setting, clinical and morphometric vertebral fractures)
High risk of vertebral fracture	200/1000	Prevalence data from Rodondi 2012 (360/1000 all grades) and Jackson 2000 (200/1000 all grades) indicate underestimate of vertebral fractures; Lindsay 2001 (mean age 74 years, fracture previous year, 200/1000)
Overall risk of non-vertebral fracture (not including hip)	20/1000	Chandler 2000 and Leslie 2011 report similar proportions of non-vertebral fractures (not including hip) to hip fractures (see 20/1000 for overall risk of hip fracture above)
High risk of non-vertebral fracture (not including hip)	60/1000	Chandler 2000 reports similar proportions of non-vertebral fractures (not including hip) to hip fractures (see 60/1000 for high risk of hip fracture above)
Falls per person per year	3	Kerse 2004 (2.6 falls [0.7 SD]); Rapp 2012 (2.8 falls in men and 1.49 falls in women)
Risk of at least 1 fall per year	500/1000	Muir 2012 review and Beauchet 2011 review of prospective/retrospective studies show rates at 12 months of 29%, 52%, 52%, 64% and 36%, 47%, 60%, 41%, 45%, 29%, respectively. Note: includes injurious and non-injurious falls
Overall risk of pelvic fractures	2/1000	O'Halloran 2004 (nursing and residential homes)
High risk of pelvic fractures	14/1000	Rapp 2009 (long term care residents)
Myocardial infarction	110/1000	Aronow 2002 (long term care residents)

Atrial fibrillation	100/1000	Reardon 2012
Major cardiovascular event	110/1000	Benetos 2012
Mortality	120/1000	Nikitovic 2012 (80+ years, range from 7 to 18%, estimate 12%; long term care 23%)
Gastrointestinal events: mild or serious	200/1000	Avenell 2009 (not LTC)
Hypercalcaemia	6/1000	Avenell 2009 (not LTC)
Renal disease (calculi or insufficiency)	17/1000	Avenell 2009 (not LTC)
Quality of life	0.7 EQ-5D	Grant 2005 (not LTC)
Hip fracture cost per person	\$36 000	Nikitovic 2012 (80+ years, community and long term care, attributal costs ranged from \$33 000 to \$39 000); Hopkins 2012 (50+ years, excess costs \$45 000 to \$46 000)
Vertebral fracture cost per person	\$6 000	Hopkins 2012 (50+ years, excess costs \$15 000 to \$19 000); Ioannidis 2013 reviewed reports of 39% of vertebral fractures, and 8 to 33% are hospitalized. Our estimates include clinical and morphometric which may not receive care. To account for fractures that would not receive care, we calculate 30% of \$19 000 = \$6 000.
Non-vertebral fracture cost per person	\$11 000	Hopkins 2012 (50+ years, excess costs for miscellaneous \$10 000 and \$14 000, humerus \$14 000 and \$11 000, wrist fractures \$8 000 and \$4 000; Chandler 2000 reports in long term care 50% miscellaneous fractures, 25% humerus and 25% wrist fractures. Therefore, from Miscellaneous \$6 000 + humerus \$3 125; wrist \$1 500 ~ \$11 000.
Myocardial infarction cost per person	\$11 500	Dhalla 2009

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Key Strategies to Prevent Fractures in Long-term Care

A4. Calcium and Vitamin D

Should vitamin D and/or calcium be recommended to prevent fractures in elderly in long term care?

A4.1 Recommendations, Remarks, and Evidence Summary

RECOMMENDATION

Calcium

For ALL RESIDENTS, we recommend dietary interventions to meet the Recommended Dietary Allowance for calcium (strong recommendation, moderate quality evidence).

Remarks: This recommendation places a high value on the reductions in fractures, mortality and falls and lower value on the resources in long-term care required to implement interventions to ensure adequate dietary intake of calcium. This recommendation is based on evidence which evaluated the effects of calcium supplements, but was used as direct evidence for dietary intake; however dietary interventions are without the side effects of supplements. The Recommended Dietary Allowance for people >70 years for calcium is 1200 mg daily which is three servings of dairy or dairy equivalents.

For residents at HIGH RISK of FRACTURES who cannot meet the Recommended Dietary Allowance for calcium through dietary intake, we recommend daily supplements of calcium up to 500 mg (strong recommendation, moderate quality evidence).

For residents who are NOT AT high RISK of fractures and who cannot meet Recommended Dietary Allowance for calcium through dietary intake, we suggest daily supplements of calcium up to 500 mg depending on resources and their (or their caregivers') values and preferences (conditional recommendation, moderate quality evidence).

Remarks: The recommendation for residents at high risk places a high value on the reduction in hip fractures, and the small reductions in vertebral and nonvertebral fractures, and mortality with calcium supplementation. It places a lower value on the small increased risk of gastrointestinal side effects which may occur and the resources required in long-term care to provide calcium supplementation. The recommendation for residents not at high risk is conditional as there may be little to no benefits of supplementation with calcium, and side effects of supplementation, such as gastrointestinal and renal side effects, may occur. For residents who value avoiding these side effects, supplementation may not be a desirable option. This recommendation applies to supplementation with any calcium compound, including calcium carbonate or citrate. The recommendation to limit supplementation to 500 mg was based on the uncertainty around harms of calcium supplementation in studies of community-dwelling individuals who received 1000 mg calcium supplementation or more daily. The benefits of calcium supplementation are closely linked to adequate vitamin D intake.

RECOMMENDATION

Vitamin D

For residents at HIGH RISK of FRACTURES, we recommend daily supplements of 800 IU to 2000 IU vitamin D₃ (strong recommendation, moderate quality evidence).

For residents NOT at high RISK of fractures, we suggest daily supplements of 800 IU to 2000 IU vitamin D₃ to meet the Recommended Dietary Allowance, depending on resources and their (or their carers') values and preferences (conditional recommendation, moderate quality evidence).

Remarks: The recommendation for residents at high risk places a high value on the reductions in hip fractures, mortality and falls, and a lower value on the long-term care resources required to provide vitamin D supplementation. The recommendation for residents not at high risk also places a high value on reduction of falls, as they may lead to serious injuries, fear of falling, and burden to staff in long-term care, but there is some uncertainty for a reduction in falls, and little to no reduction in fractures with vitamin D supplementation in this group. This recommendation applies to supplementation with D₃, as D₃ may be more accessible due to lower costs compared to D₂. A dose of approximately 800 IU was found to reduce fractures in people with normal and low 25-hydroxyvitamin D levels and also increase 25-hydroxyvitamin D levels to normal in those who had low levels, therefore 800 IU is recommended. However, the exact dose may depend on the dosing regimen that is available (e.g. a 1000 IU drop or tablet would be acceptable). The benefits of vitamin D supplementation are closely linked to adequate calcium intake, and therefore recommendations for calcium intake should also be applied. The Recommended Dietary Allowance for vitamin D for people >70 years is 800 IU daily and the Tolerable Upper Intake Level up to 4000 IU.

Evidence summary: Overall there was moderate quality evidence for benefits and low to very low quality evidence for harms. We found that vitamin D in addition to calcium probably reduces hip fractures and mortality more than vitamin D alone or calcium alone (Avenell 2009; Bischoff-Ferrari 2012; Murad 2012): for residents at high risk we estimated 15/1000 (95% CI, -5 to -24) fewer hip fractures; for residents not at high risk 5/1000 (95% CI, -2 to -8) fewer hip fractures; and for all residents 7/1000 fewer deaths (95% CI, 1 to 14). We found vitamin D and calcium supplementation probably has little or no effect on vertebral fractures with only 2/1000 (95% CI, -44 to 61) fewer vertebral fractures, and this is similar with vitamin D only, but probably a greater reduction with calcium only (49/1000, 95% CI -99 to 9)(Avenell 2009; Murad 2012). Calcium, or vitamin D with or without calcium, probably has little to no effect on the incidence of nonvertebral fractures (Avenell 2009; Bischoff-Ferrari 2012; Murad 2011), quality of life (Grant 2005) or muscle strength (Muir 2011). The data for falls was not precise (wide confidence intervals including benefit, no effect and harm) and the effects were not consistent when measuring rate of falls or risk of falls (Cameron 2012; Gillespie 2012; Murad 2011; Reid 2006). However, vitamin D and calcium, or vitamin D alone may reduce falls, and one-third of all falls may result in an injury and every fifth injurious fall may result in treatment outside the

patient's own setting (Nurmi 2002). There were no data on pain, anxiety, mobility and activities of daily living (ADL) performance.

With respect to minor and major adverse events, vitamin D or calcium supplements probably similarly increase mild or serious gastrointestinal events, approximately 8/1000 more (95% CI 0 to 17) (Avenell 2009). Gastrointestinal symptoms or difficulties taking calcium tablets may contribute to poor compliance (Grant 2005; Reid 2006). Vitamin D (D₂ and D₃) with calcium may cause slightly more hypercalcemia (5 more, 95% CI -1 to 18) and renal insufficiency or calculi (3/1000, 95% CI 0 to 6) (Avenell 2009). The evidence for greater myocardial infarctions with supplementation of calcium \geq 1000 mg in community-dwelling individuals is uncertain as it is not consistent with the reductions in mortality (Avenell 2009), and the confidence intervals around the estimates include no effect, and the possibility of appreciable harm (Bolland 2010; Bolland 2011; Elamin 2011).

Subgroup analyses from systematic reviews found that there may be little or no difference in fractures or falls by type of vitamin D (D₃ or D₂) (Avenell 2009; Levis 2012; Murad 2011); there may be greater benefits with vitamin D >792 IU (actual intake in most studies was between 792-844 IU), but no difference with < or >1000 mg Ca, and there are inconsistent effects when vitamin D is given in large doses monthly or annually (Bischoff-Ferrari 2012; Bischoff-Ferrari 2009). Analyses did find that vitamin D may have greater effects on reducing falls (Gillespie 2012; Murad 2011) and fractures in people with low vitamin D status (Bischoff-Ferrari 2012). Autier 2012 (Autier 2012) also found that approximately 800 IU provided over several months can increase serum vitamin D levels to 'normal' levels in people that are deficient (e.g. 25 nmol/L).

A4.2 Question, Evidence to Recommendations Table (Calcium and Vitamin D)

QUESTION

Population	Elderly in long term care (LTC)*
Intervention	Vitamin D and/or calcium to prevent fractures
Comparison	No vitamin D or calcium
Outcomes	Hip fractures, vertebral and other fractures, pain, agitation, mobility, independence for activities of daily living (qol), mortality, resource use or costs, acceptability, severe adverse events, minor adverse events requiring medical attention

* Long term care can refer to the following depending on country: Long Term Care Home, Retirement Home, Nursing Home, Skilled Nursing Facility, Care Home, Care Home (with Nursing), Residential Aged Care Facility, and Hostels.

Decision domain:	Explanation	Summary of reason for judgement	Judgement
<p>Quality of evidence (QoE) <i>Is there high or moderate quality evidence?</i> The higher the quality of evidence, the more likely is a strong recommendation</p>	<p>QoE for benefits: Moderate QoE for harms: High to low QoE for resource use: Low Key reasons for downgrading the evidence: Risk of bias and indirectness as not long term care (LTC) population – but there did not appear to be differences between LTC and community settings in most subgroup analyses. There was not enough data to conduct analyses on populations at high risk versus overall risk of hip fractures. Myocardial infarction was low quality due to inconsistency with effects on mortality.</p>		<p>Yes No <input type="checkbox"/> <input checked="" type="checkbox"/></p>
<p>Balance of benefits versus harms and burdens <i>Are you confident that the benefits outweigh the harms and burden or vice versa?</i> The larger the difference between the benefits and harms and the certainty around that difference, the more likely is a strong recommendation. The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional recommendation.</p>	<p>Vitamin D with calcium (compared to vit D or Ca alone) Probably reduces hip fractures more than vitamin D or calcium alone: in low risk groups reduces 5/1000 (-2 to -8); in high risk groups reduces 15/1000 (-5 to -24) Probably little or no effect on vertebral fractures (2/1000 fewer, -44 to 61); similar to vitamin D alone, however probably greater reduction with calcium alone (49/1000 fewer, -99 to 19 more) Probably has little to no effect on nonvertebral fractures, quality of life and strength (similar to vitamin D or calcium alone) May reduce falls (likely similar to vitamin D alone, but greater than calcium alone) Probably reduces mortality more: reduces 7/1000 (1 to 14) May be similar effects on myocardial infarction across supplements, including no effect or increase with ≥ 1000 mg calcium Probably has similar effect on mild or serious GI events (increase 8/1000, 0 to 17); may cause slightly more hypercalcemia (5 more, -1 to 18) and renal insufficiency or calculi (3/1000, 0 to 6) No data on pain, anxiety, mobility and ADL</p> <p>There may be little or no difference on fractures or falls by type of vitamin D (D₃ or D₂) (Avenell 2009, AHRQ 2012, Murad 2011); Effects with Vit D intake >792 IU, no difference with <1000 or >1000mg Ca, and may have little effect when dose given annually (Bischoff-Ferrari 2009, 2012). Vitamin D may have greater effects on falls in people with low vitamin D levels (Gillespie 2012, Murad 2011). Reductions in hip and nonvertebral fractures may be greater in people with low vitamin D levels (<30 nmol/liter) when actual intake is between 792-2000 IU (actual intake in most studies was between 792-844 IU) (Bischoff-Ferrari 2012). Approximately 800 IU provided over several</p>	<p>In high risk elderly, benefits of vitamin D with calcium slightly outweigh harms (little to no side effects, such as GI and renal, and the uncertain risk of myocardial infarctions at 1000 mg or more calcium).</p> <p>In elderly not at high risk, benefits of vitamin D with calcium may be balanced with harms (little to no side effects, such as GI and renal, and the uncertain risk of myocardial infarctions at 1000 mg or more calcium).</p> <p>In elderly at any risk, the little to no benefits of vitamin D alone or calcium alone are balanced with harms.</p>	<p>High risk Yes No X <input type="checkbox"/></p> <p>Not at high risk Yes No <input type="checkbox"/> X</p>

	<p>months can increase serum vitamin D levels to 'normal' levels in people that are deficient (e.g. 25 nmol/L) (Autier 2012). However, an AHRQ report concluded that the associations between serum 25OHD concentrations and risk of fractures are inconsistent in post-menopausal women or elderly men; and there was fair evidence of association with increased risk of falls and serum 25OHD levels in institutionalised elderly.</p> <p>IOM recommendations and Canadian RDA (>70 years): Vitamin D: ERA 400IU, RDA 800 IU Calcium: ERA 1000 mg, RDA 1200 mg</p>																														
<p>Values and preferences <i>Are you confident about the assumed or identified relative values and are they similar across the target population?</i> The more certainty or similarity in values and preferences, the more likely a strong recommendation</p>	<p>AHRQ review found no association between a history of prior fractures with compliance to osteoporosis medications. Grant 2005 found poor compliance associated with stopping due to gastrointestinal symptoms or difficulties taking tablets.</p> <p>Consequences of hip fracture: LTC with fracture 50-80% increased mortality risk over LTC with no fracture; 65% lose mobility; meaningful loss in quality of life.</p> <p>One-third of all falls may result in an injury and every fifth injurious fall may result in treatment outside the patient's own setting (Nurmi 2002).</p>	<p>High value on avoiding hip fractures and falls which may result in serious injury, fear of falling, and burden to staff.</p> <p>Low value on small and uncertain risk of side effects. However, all side effects of supplements would be avoided with adequate dietary intake.</p>	<p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>																												
<p>Resource implications <i>Are the resources worth the expected net benefit from following the recommendation?</i> The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention.</p>	<table border="1"> <thead> <tr> <th colspan="4">Annual cost per 1000 elderly at high risk of fractures</th> </tr> <tr> <th></th> <th>Vit D alone</th> <th>Vit D with calcium</th> <th>Calcium alone</th> </tr> </thead> <tbody> <tr> <td><i>Supplement (≥800 IU D₃, ≥500mg Ca)</i></td> <td>\$72,000</td> <td>\$136,000</td> <td>\$64,000</td> </tr> <tr> <td><i>Hip fracture</i></td> <td>-\$216,000</td> <td>-\$540,000</td> <td>\$288,000</td> </tr> <tr> <td><i>Vertebral fracture</i></td> <td>-\$36,000</td> <td>-\$12,000</td> <td>-\$294,000</td> </tr> <tr> <td><i>Nonvertebral fracture</i></td> <td>\$11,000</td> <td>-\$33,000</td> <td>\$0</td> </tr> <tr> <td>TOTAL</td> <td>-\$241,000</td> <td>-\$585,000</td> <td>-\$6,000</td> </tr> </tbody> </table>	Annual cost per 1000 elderly at high risk of fractures					Vit D alone	Vit D with calcium	Calcium alone	<i>Supplement (≥800 IU D₃, ≥500mg Ca)</i>	\$72,000	\$136,000	\$64,000	<i>Hip fracture</i>	-\$216,000	-\$540,000	\$288,000	<i>Vertebral fracture</i>	-\$36,000	-\$12,000	-\$294,000	<i>Nonvertebral fracture</i>	\$11,000	-\$33,000	\$0	TOTAL	-\$241,000	-\$585,000	-\$6,000	<p><i>Costs of supplements not consistently funded across provinces. However, costs appeared worth the net benefit in elderly at high risk of fractures.</i></p>	<p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>
Annual cost per 1000 elderly at high risk of fractures																															
	Vit D alone	Vit D with calcium	Calcium alone																												
<i>Supplement (≥800 IU D₃, ≥500mg Ca)</i>	\$72,000	\$136,000	\$64,000																												
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<i>Nonvertebral fracture</i>	\$11,000	-\$33,000	\$0																												
TOTAL	-\$241,000	-\$585,000	-\$6,000																												

BASELINE COSTS

Annual cost per 1000 elderly			
	Vit D alone	Vit D with calcium	Calcium alone
<i>Supplement (≥800 IU D₃, ≥500mg Ca)</i>	\$72,000	\$136,000	\$64,000
<i>Hip fracture</i>	\$72,000	-\$180,000	\$108,000
<i>Vertebral fracture</i>	-\$6,000	\$0	-\$36,000
<i>Nonvertebral fracture</i>	\$0	-\$11,000	\$0
TOTAL	\$66,000	-\$191,000	\$72,000

A4.3 Evidence Profile

Vitamin D with/without calcium for people at risk of fractures in long term care to prevent fractures

Outcomes	Effects and Quality of the Evidence						
	Vitamin D without calcium		Vitamin D with calcium		Calcium	Placebo/no treatment	
Hip fractures	OR 1.10 (0.88 to 1.37)	Overall risk	OR 0.73 (0.59 to 0.91)	Overall risk	OR 1.14 (0.82 to 1.59)	Overall risk	
		2 more per 1000 (3 fewer to 7 more)		5 fewer per 1000 (2 to 8 fewer)		3 more per 1000 (4 fewer to 11 more)	20 hip fractures per 1000
		High risk		High risk		High risk	High risk
		6 more per 1000 (10 fewer to 20 more)		15 fewer per 1000 (5 to 24 fewer)		8 more per 1000 (10 fewer to 32 more)	60 hip fractures per 1000
	Based on 7225 participants, 3 trials		Based on 3853 participants, 2 trials		Based on 139 647 participants, 40 trials		
	⊕⊕⊕⊖ moderate Risk of bias: high loss to follow-up and lack of blinding, although consistent results in Avenell 2009 (institution and community) and Murad 2012		⊕⊕⊕⊖ moderate Risk of bias: high loss to follow-up, high event rates, unclear blinding, although consistent in Avenell 2009 (institution and community), Murad 2012, and Bischoff-Ferrari 2012		⊕⊕⊕⊖ moderate From network meta-analysis with trials with risk of bias; population primarily community (Murad 2012)		
Vertebral fractures	OR 0.96 (0.59 to 1.58)	Overall risk	OR 0.99 (0.74 to 1.41)	Overall risk	OR 0.71 (0.45 to 1.12)	Overall risk	
		1 fewer per 1000 (8 fewer to 11 more)		0 fewer per 1000 (5 fewer to 8 more)		6 fewer per 1000 (11 fewer to 2 more)	20 vertebral fractures per 1000
		High risk		High risk		High risk	High risk
		6 fewer per 1000 (71 fewer to 83 more)		2 fewer per 1000 (44 fewer to 61 more)		49 fewer per 1000 (99 fewer to 19 more)	200 vertebral fractures per 1000
	Based on 139 647 participants, 40 trials		Based on 139 647 participants, 40 trials		Based on 139 647 participants, 40 trials		
	⊕⊕⊕⊖ moderate From network meta-analysis (Murad 2012) with trials with risk of bias; population primarily community; consistent with Avenell 2009		⊕⊕⊕⊖ moderate From network meta-analysis (Murad 2012) with trials with risk of bias; population primarily community; consistent with Avenell 2009		⊕⊕⊕⊖ moderate From network meta-analysis (Murad 2012) with trials with risk of bias; population primarily community; consistent with Avenell 2009		

Outcomes	Effects and Quality of the Evidence						
	Vitamin D without calcium		Vitamin D with calcium		Calcium	Placebo/no treatment	
Nonvertebral fractures		Overall risk 0 more per 1000 (3 fewer to 4 more)		Overall risk 1 fewer per 1000 (3 fewer to 0)		Overall risk 0 fewer per 1000 (3 fewer to 4 more)	Overall risk 20 nonvertebral fractures per 1000
	OR 1.01 (0.85 to 1.20)	High risk 1 more per 1000 (9 fewer to 11 more)	OR 0.94 (0.84 to 1.02)	High risk 3 fewer per 1000 (9 fewer to 1 more)	OR 1.00 (0.83 to 1.22)	High risk 0 fewer per 1000 (10 fewer to 12 more)	High risk 60 nonvertebral fractures per 1000
	Based on 139 647 participants, 40 trials ⊕⊕⊕⊖ moderate From network meta-analysis (Murad 2012) with trials with risk of bias; population primarily community		Based on 139 647 participants, 40 trials ⊕⊕⊕⊖ moderate From network meta-analysis (Murad 2012) with trials with risk of bias; population primarily community; greater reductions found in Avenell 2008 and Bischoff-Ferrari 2012 in institutions		Based on 139 647 participants, 40 trials ⊕⊕⊕⊖ moderate From network meta-analysis (Murad 2012) with trials with risk of bias; population primarily community		
Number of falls per 1000 people	Rate Ratio 0.55 (0.19 to 1.64)	1350 fewer falls per 1000 people (2430 fewer to 1920 more)	Rate Ratio 0.96 (0.89 to 1.04)	120 fewer falls per 1000 people (330 fewer to 120 more)	"No difference"		3000 falls per 1000 people per year
	Based on 3765 participants, 2 trials ⊕⊕⊖⊖ low Risk of bias, imprecision due to few participants (Cameron 2012); results in community and institution vitamin D alone and with calcium from Murad 2011 OR 0.79, 0.70–0.88.		Based on 6586 participants, 3 trials ⊕⊕⊖⊖ low Risk of bias, indirect: community only, greater reduction in people with low vitamin D levels (Gillespie 2012); results in community and institution vitamin D alone and with calcium from Murad 2011 OR 0.79, 0.70–0.88.		Based on 1471 participants, 1 trial ⊕⊕⊖⊖ low Indirect: community only; imprecise; 595 falls per 1000 with calcium, 585 with placebo (Reid 2006)		
Number of people who fell at least once per year	OR 0.80 (0.38 to 1.71)	56 fewer per 1000 (225 fewer to 131 more)	OR 1.03 (0.90 to 1.18)	7 more per 1000 (26 fewer to 41 more)	"no difference"		500 people per 1000

Based on 3765 participants, 2 trials	Based on 583 participants, 1 trial	Based on 2643 participants, 1 trial	
⊕⊕⊕⊕ low Risk of bias, imprecision (Cameron 2012); consistent with Murad 2011, all population 0.97(0.84-1.11)	⊕⊕⊕⊕ moderate Risk of bias (Cameron 2012); consistent with Murad 2011, all population 0.83 (0.72-0.93); more benefit in people with lower vitamin D levels.	⊕⊕⊕⊕ low Indirect: community only, measured 1 week after 4 months; imprecise; HR 0.89 (0.77–1.02) (Grant 2005)	

Outcomes	Effects and Quality of the Evidence				Placebo/no treatment
	Vitamin D without calcium	Vitamin D with calcium	Calcium		
Strength, gait, balance	Little to no effect in favour of vitamin D	Little to no effect in favour of vitamin D	“significant difference in grip strength in favour of calcium”		-
	Based on <600 participants, 3 trials per outcome ⊕⊕⊕⊕ very low Indirect: mixed population; imprecise; publication bias (Muir 2011)	Based on <600 participants, 3 trials per outcome ⊕⊕⊕⊕ very low Indirect: mixed population; imprecise; publication bias (Muir 2011)	Based on 1471 participants, 1 trial ⊕⊕⊕⊕ very low Indirect: community only; imprecise; (Muir 2011)		
Mortality	OR 1.01 (0.92 to 1.11) 1 more per 1000 (9 fewer to 11 more)	OR 0.93 (0.87 to 0.99) 7 fewer per 1000 (1 to 14 fewer)	OR 1.07 (0.95 to 1.19) 8 more per 1000 (6 fewer to 23 more)		120 deaths per 1000
	Based on 8767 participants, 3 trials ⊕⊕⊕⊕ moderate Risk of bias; inconsistency among trials; data for institutional setting (Avenell 2009)	Based on 5919 participants, 6 trials ⊕⊕⊕⊕ moderate Risk of bias, data for institutional setting (Avenell 2009); some inconsistency with Bolland 2010 community only (RR 1.01, 0.90 to 1.12)	Based on 10826 participants, 10 trials ⊕⊕⊕⊕ moderate Risk of bias; indirect as community only (Bolland 2010)		
Quality of life EQ-5D (Scale: 0 to 1, optimal health) or SF12 2 years	No differences in quality of life. Based on 5292 participants, 1 trial ⊕⊕⊕⊕ moderate Indirect: community only (Grant 2005)	No differences in quality of life. Based on 5292 participants, 1 trial ⊕⊕⊕⊕ moderate Indirect: community only (Grant 2005)	No differences in quality of life. Based on 5292 participants, 1 trial ⊕⊕⊕⊕ moderate Indirect: community only (Grant 2005)		0.7 on EQ-5D
	RR 1.02 (0.93 to 1.13) 2 more per 1000 (8 fewer to 14 more)	RR 1.21 (1.01 to 1.44) 23 more per 1000 (1 to 48 more)	RR 1.27 (1.01 to 1.59) 30 more per 1000 (1 to 65 more)		110 MI per 1000

<p>Based on 39 879 participants, 6 trials</p> <p>⊕⊕⊕⊕ low</p> <p>Risk of bias; indirect as community only in Elamin 2011– some include calcium in both groups; inconsistent with mortality; dosages at 1000 mg calcium or more</p>	<p>Based on 20 090 participants, 3 trials</p> <p>⊕⊕⊕⊕ low</p> <p>Risk of bias; indirect as community only in Bolland 2011–most not taking calcium before; inconsistent with mortality; dosages at 1000 mg calcium or more</p>	<p>10210 participants, 6 trials</p> <p>⊕⊕⊕⊕ low</p> <p>Risk of bias; indirect as community only in Bolland 2010–some studies with vitamin D; inconsistent with mortality; dosages at 1000 mg calcium or more</p>	
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Outcomes	Effects and Quality of the Evidence					
	Vitamin D without calcium		Vitamin D with calcium		Calcium	Placebo/No treatment
Gastro-intestinal events (mild or serious)	OR 1.05 (1.00 to 1.10)	8 more per 1000 (0 to 17 more)	OR 1.05 (1.00 to 1.10)	8 more per 1000 (0 to 17 more)	Participants reported more with calcium carbonate (1 g; includes Vitamin D) vs placebo; more constipation with calcium citrate (1 g) vs placebo	
	Based on 7764 participants, 7 trials ⊕⊕⊕⊕ high Vitamin D with/without calcium analysis combined as no differences (Avenell 2009)		Based on 7764 participants, 7 trials ⊕⊕⊕⊕ high Vitamin D with/without calcium analysis combined as no differences (Avenell 2009)		Based on 2643 and 1471 participants, 2 trials ⊕⊕⊖⊖ low Imprecise; indirect community (Grant 2005 and Reid 2006)	
Hypercalcaemia	OR 1.04 (0.16 to 6.73)	0 more per 1000 (5 fewer to 33 more)	OR 1.84 (0.82 to 4.13)	5 more per 1000 (1 fewer to 18 more)	No difference	0 more per 1000
	Based on 3034 participants, 2 trials ⊕⊕⊖⊖ low Risk of bias; indirect- community and institution; Imprecise – very few events (Avenell 2009)		Based on 6583 participants, 6 trials ⊕⊕⊖⊖ low Risk of bias; indirect- community and institution; Imprecise – very few events (Avenell 2009)		Based on 2643 participants, 1 trial ⊕⊕⊖⊖ low Indirect- community only; Imprecise – very few events (Grant 2005 and Reid 2006)	
Renal disease (calculi or insufficiency)	OR 0.66 (0.03 to 16.20)	6 fewer per 1000 (16 fewer to 202 more)	OR 1.17 (1.02 to 1.34)	3 more per 1000 (0 to 6 more)	No difference	0 more per 1000
	Based on 393 participants, 1 trial ⊕⊖⊖⊖ very low Risk of bias; indirect- community; Imprecise – very few events (Avenell 2009)		Based on 41574 participants, 2 trials ⊕⊕⊕⊖ moderate Indirect- community only in analysis; (Avenell 2009)		Based on 2643 and 1471 participants, 2 trials ⊕⊕⊖⊖ low Imprecise; indirect community (Grant 2005 and Reid 2006)	

A4.4 Resources used to inform the recommendations

Systematic reviews and reviews

- Agency for Healthcare Research and Quality: Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report. Comparative Effectiveness Review Number 53. March 2012.
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prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab.* 2012 Jun;97(6):1871-80.

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Randomised controlled trials

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A5. Pharmacological Therapies

Should pharmacological therapies to prevent fractures be recommended for elderly in long term care?

A5.1 Recommendations, Remarks, and Evidence Summary

RECOMMENDATION

For residents who are at HIGH RISK of FRACTURES, we recommend alendronate (weekly) or risedronate (weekly or monthly) be used as first line therapies (strong recommendation, moderate quality evidence).

Remarks: The probable reduction in fractures (hip, vertebral and nonvertebral) and mortality with alendronate or risedronate outweigh the low or uncertain risk of harms or side effects, such as atypical femur fractures. Alendronate and risedronate are first line therapies because of their relatively low costs compared to other therapies. Alendronate and risedronate are not to be crushed, and are to be provided to elderly who have an empty stomach and can remain upright for 30 minutes after administration. Some formulations must be administered at least 30 minutes before food intake. Other formulations can be taken with food. For the elderly who cannot swallow or have difficulty taking oral medications, alternative first line therapies are available (see recommendations for denosumab and zoledronic acid). The product monographs indicate that alendronate and risedronate are not recommended for elderly with severe renal insufficiency (creatinine clearance <35 mL/min or <30 mL/min, respectively).

For residents who are at HIGH RISK of FRACTURES and HAVE DIFFICULTY TAKING ORAL MEDICATIONS, we recommend zoledronic acid be used as first line therapy (strong recommendation, moderate quality evidence).

Remarks: The probable reduction in fractures (hip, vertebral and nonvertebral) and mortality with zoledronic acid slightly outweighs the uncertain increased risk of musculoskeletal side effects (e.g. arthralgia, myalgia) and the costs when compared to other first line therapies. This recommendation applies to the elderly who have difficulty taking oral medications due to dysphagia, an inability to sit up for 30 minutes, cognitive impairment, or intolerance. The product monograph indicates that infusion should be performed over no less than 15 minutes. Health Canada advises that caution is necessary for people who receive other medications that could impact renal function; creatinine clearance should be monitored before and periodically after treatment; appropriate hydration before and after treatment (500 mL of water) is necessary; and it should not be used in people with severe renal impairment (creatinine clearance <30 mL/min).

For residents who are at HIGH RISK of FRACTURES and have DIFFICULTY TAKING ORAL MEDICATIONS, we recommend denosumab be used as first line therapy (strong recommendation, moderate quality evidence).

Remarks: The reduction in fractures (hip, vertebral and nonvertebral) and mortality with denosumab slightly outweigh the small and uncertain risk of serious infections and greater costs compared to other first line therapies. This recommendation applies to elderly who have difficulty taking oral

medications due to dysphagia, an inability to sit up for 30 minutes, cognitive impairment, or intolerance. While denosumab can be prescribed to residents with renal impairment, they are at higher risk of developing hypocalcemia. The product monograph indicates in clinical studies, patients with renal impairment (creatinine clearance <30mL/min) or receiving dialysis were at greater risk of developing hypocalcemia.

For residents who are at HIGH RISK OF FRACTURES, we suggest teriparatide (conditional recommendation, moderate quality evidence).

Remarks: Although the benefits of teriparatide (in particular on vertebral fractures) probably outweigh harms of treatment, the cost of therapy restricts its access, and there may be a higher burden due to daily injections. A low value was placed on the uncertain effect of teriparatide on back pain due to past and future vertebral fractures, and on hip fractures.

For residents who are at HIGH RISK of FRACTURES, we suggest raloxifene not be used (conditional recommendation, moderate quality evidence).

Remarks: The harms of raloxifene (such as venous thromboembolism and musculoskeletal events e.g. arthralgia, myalgia) probably outweigh the probable reduction in vertebral fractures and small reductions in hip and nonvertebral fractures.

For residents who are at HIGH RISK of FRACTURES, we suggest etidronate not be used (conditional recommendation, moderate quality evidence).

Remarks: There is moderate quality evidence for little to no reduction in fractures (in particular hip fractures). The cost is also high relative to the lack of important benefits.

Evidence summary: There is moderate quality evidence from network meta-analyses of randomised controlled trials in over 100 000 people at high risk of fractures (Hopkins 2011; AHRQ 2012; Murad 2011). There was risk of bias in some studies and uncertainty when applying effects in post-menopausal women to long-term care residents. Results showed probable reductions in hip fractures of approximately **25/1000 fewer** across drugs, but relatively smaller reductions with etidronate and raloxifene. Evidence also shows probable reductions in vertebral fractures (approximately **100/1000 fewer**) and non-vertebral fractures (approximately **20/1000 fewer**) with all drugs, but relatively greater reductions with teriparatide, and smaller reductions with raloxifene. Systematic reviews also showed probable reductions in mortality with oral bisphosphonates (10/1000 fewer, 95% CI -22 to 3) and raloxifene (10/1000 fewer, 95% CI -21 to 0); but there may be a greater reduction denosumab (**23/1000 fewer 95% CI -46 to 6**) (Bolland 2010). Other benefits based on low quality evidence may include a small reduction in back pain related to past and future vertebral fractures for teriparatide (Nevitt 2006), but there was little to no effect on quality of life for other therapies (Hadji 2012; Jacobsen 2012; Nevitt 2006; Sambrook 2011; Silverman 2012).

There was low to very low quality evidence for very small risks of serious events such as osteonecrosis of the jaw and atypical fractures/delayed healing (estimated at <1/10 000 in community dwelling elderly) (Rizzoli 2011; Rizzoli 2007; Rizzoli 2011). It is unclear whether these risks would be higher in long-term care residents. Evidence is also low quality for the risk of atrial fibrillation with bisphosphonates (Mak 2009), and cerebrovascular/cardiovascular events with raloxifene (Grady 2010): results are imprecise and include the possibility of small to no increase in these events. Venous

thromboembolism may increase with raloxifene (12/1000 more, 95% CI 7 to 19))(Grady 2010); musculoskeletal events may increase with zoledronic acid (146/1000 more,95% CI 125 to 169) (Hadji 2012); and serious infections may increase with denosumab (8/1000 more, 95% CI 0 to 18)) (Toulis 2010). Randomised controlled trials and pharmacovigilance for bisphosphonates and raloxifene showed little to no effect of the drugs on serious gastrointestinal events (AHRQ 2012).

Direct drug costs were worth the overall beneficial consequences of most drugs with the exception of etidronate and raloxifene. Costs of teriparatide, denosumab and zoledronic acid were also high relative to the other therapies.

A5.2 Question, Evidence to Recommendations Table regarding Osteoporosis Pharmacological Therapies, Costs

QUESTION

Population	Elderly in long term care*
Intervention	Drug therapies: bisphosphonates (alendronate, risedronate and zoledronate); etidronate; teriparatide; raloxifene; denosumab. Drug therapies not currently available in Canada were not reviewed.
Comparison	No drug therapy (or placebo)
Outcomes	Hip fractures, vertebral and other fractures, pain, agitation, mobility, independence for activities of daily living (quality of life), mortality, resource use, acceptability, costs, severe adverse events, minor adverse events requiring medical attention

*Long term care can refer to the following depending on country: Long Term Care Home, Retirement Home, Nursing Home, Skilled Nursing Facility, Care Home, Care Home (with Nursing), Residential Aged Care Facility, and Hostels.

Decision domain:	Explanation	Summary of reason for judgement	Judgement
<p>Quality of evidence (QoE) <i>Is there high or moderate quality evidence?</i> The higher the quality of evidence, the more likely is a strong recommendation</p>	<p>QoE for benefits: moderate to low QoE for harms: low to very low QoE for resource use: low Key reasons for downgrading the evidence: Indirect - data primarily for women with established or at risk of osteoporosis in the community setting; some concern with risk of bias of studies and reporting of secondary outcomes Little to no data for pain, agitation, mobility, independence for activities of daily living, quality of life.</p>		<p>Yes No <input type="checkbox"/> X</p>
<p>Balance of benefits versus harms and burdens <i>Are you confident that the benefits outweigh the harms and burden or vice versa?</i> The larger the difference between the benefits and harms and the certainty around that difference, the more likely is a strong recommendation. The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional recommendation.</p>	<p>Probable reductions for hip fractures consistent across drugs (~25 fewer per 1000), although relatively smaller reduction with etidronate and raloxifene Reductions for vertebral (~100 fewer per 1000) and non-vertebral fractures (~20 fewer per 1000) but relatively greater reductions with teriparatide, and smaller with raloxifene</p> <p>Probably reductions in mortality across all drugs with ~10 fewer with bisphosphonates and raloxifene; may be greater reduction with denosumab (23 fewer)</p> <p>May have little to no effect on quality of life, but probable reduction in back pain reported for teriparatide</p> <p>Cardiovascular events may be increased with bisphosphonates (54 more per 1000) and raloxifene (19 more); venous thromboembolism may be increased with raloxifene (12 more); and musculoskeletal events increased with zoledronate (146 more); little to no effect on gastrointestinal events for bisphosphonates and raloxifene; serious infections may be increased with denosumab; and uncertain effect of teriparatide on back pain.</p> <p>Burden of therapies to staff and/or elderly: zoledronate providing once per year with skilled care and sitting up for 45 minutes; oral alendronate and risedronate difficult to swallow and routine for delivery (e.g. before meals and 30 minutes sitting up after taking); teriparatide injections daily; and denosumab subcutaneous injection.</p>	<p>For most therapies, benefits clearly outweigh harms. Risks of harms may occur or are uncertain due to few long term studies or post-marketing.</p> <p>However, there were very small and/or uncertain benefits with etidronate and raloxifene.</p>	<p>Yes No X <input type="checkbox"/></p> <p>Yes No <input type="checkbox"/> X</p>

<p>Values and preferences <i>Are you confident about the assumed or identified relative values and are they similar across the target population?</i> The more certainty or similarity in values and preferences, the more likely a strong recommendation.</p>	<p>Review reported preference for less frequent dosing preferred (weekly over daily; annually over weekly, IV over oral), but side effects more important than frequency (also regardless of efficacy).</p> <p>Downstream consequences of hip fractures: 50-80% greater mortality; 65% lose mobility; meaningful loss in quality of life.</p>	<p>High value was placed on avoiding serious consequences of fractures. Low value was placed on minor side effects (e.g. gastrointestinal) or uncertain side effects (e.g. serious infections).</p>	<p>Yes No X <input type="checkbox"/></p>
<p>Resource implications <i>Are the resources worth the expected net benefit from following the recommendation?</i> The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention.</p>	<p>Costs were estimated using over-the-counter wholesale costs to provide relative costs across drugs. Costs for dispensing, etc. not provided. Costs likely vary provincially.</p> <p>See Table page 27-28.</p>	<p>Costs of teriparatide, denosumab and zoledronate were high relative to the other therapies leading to recommendations for those therapies in high risk elderly who could not take oral medications.</p>	<p>Yes No X <input type="checkbox"/></p>

BASELINE RISKS AND COSTS

See A3. Pg 9 and 10 for estimates regarding the risk of fractures among those at high risk of fracture and among all elderly LTC residents. Estimates regarding costs associated with treating fractures are also listed.

Note: The absolute risks of outcomes with drug therapies were calculated by applying the relative effects of each drug therapy on the risk of an outcome in a high risk population taking Vitamin D and Calcium. The risks when taking Vitamin D and Calcium were calculated by applying the relative effects of Vitamin D and Calcium on baseline risks (with no treatment). See Vitamin D and calcium evidence profile for more information.

Annual Costs of pharmacologic therapy (CDN) per person for elderly in long term care

These costs are based on data from *wholesale drug costs (2012)* and were used to estimate relative costs across available pharmacologic therapies.

	Annual Estimate
Drugs including cost of Vitamin D \geq 800 IU and Calcium \geq 500 mg (2012)	
- Alendronate (70 mg weekly)	\$270
- Risedronate Sodium (35 mg weekly)	\$270
- Risedronate Sodium (150 mg monthly)	\$520
- Zoledronic acid (5 mg/100 ml annually)	\$810
- Etidronate disodium/Calcium Carbonate (400 mg/500 mg annually)	\$150
- Teriparatide (daily)	\$9140
- Raloxifene (60 mg daily)	\$560
- Denosumab (60 ml/mg q 6 months)	\$820

ANNUAL COSTS per 1000 elderly in long term care at HIGH risk of fractures

	Alendronate	Risedronate weekly	Risedronate monthly	Zoledronate	Etidronate	Teriparatide	Raloxifene	Denosumab
Drug	270,000	270,000	520,000	810,000	150,000	9,140,000	560,000	820,000
Hip (\$36,000)	-900,000	-828,000	-828,000	-828,000	36,000	-936,000	-216,000	-828,000
Vertebral (\$6,000)	-600,000	-648,000	-648,000	-780,000	-468,000	-840,000	-516,000	-804,000
Nonvertebral (\$11,000)	-143,000	-209,000	-209,000	-209,000	-242,000	-330,000	-66,000	-176,000
Other adverse events (not estimated)								
	-							
TOTAL ("“ savings)	1,373,000	-1,415,000	-1,165,000	-1,007,000	-524,000	7,034,000	-238,000	-988,000
	0							

A5.3 Evidence Profile

Drug therapies to prevent fractures for elderly at HIGH risk of fractures in long term care

Outcomes	Effects and Quality of the Evidence							
	Bisphosphonates (primarily with at least 500 mg calcium, and with/without vitamin D)				Teriparatide (with calcium and vitamin D)	Raloxifene (with/without calcium and vitamin D)	Denosumab (with calcium and vitamin D)	No drug therapy with calcium and Vitamin D
	Alendronate	Risedronate	Zoledronate	Etidronate				
Hip fractures	OR 0.45 (0.27 to 0.68)	OR 0.48 (0.31 to 0.66)	OR 0.50 (0.34 to 0.73)	OR 1.02 (0.12, 3.91)	OR 0.42 (0.10 to 1.82)	OR 0.87 (0.63 to 1.22)	OR 0.50 (0.27 to 0.86)	45 hip fractures per 1000
	24 fewer per 1000 (14 to 32 fewer)	23 fewer per 1000 (15 to 31 fewer)	22 fewer per 1000 (12 to 29 fewer)	1 more per 1000 (39 fewer to 111 more)	26 fewer per 1000 (40 fewer to 34 more)	6 fewer per 1000 (16 fewer to 9 more)	22 fewer per 1000 (6 to 32 fewer)	(no calcium or Vitamin D - 60 hip fractures per 1000)
Vertebral fractures	OR 0.50 (0.33 to 0.79)	OR 0.46 (0.31 to 0.68)	OR 0.35 (0.20 to 0.64)	OR 0.61 (0.29 to 1.08)	OR 0.30 (0.16 to 0.55)	OR 0.57 (0.39 to 0.83)	OR 0.33 (0.19 to 0.65)	200 vertebral fractures per 1000
	89 fewer per 1000 (35 to 124 fewer)	97 fewer per 1000 (55 to 128 fewer)	120 fewer per 1000 (62 to 152 fewer)	68 fewer per 1000 (132 fewer to 13 more)	130 fewer per 1000 (79 to 162 fewer)	75 fewer per 1000 (28 to 111 fewer)	124 fewer per 1000 (60 to 155 fewer)	
Nonvertebral fractures	OR 0.78 (0.66 to 0.92)	OR 0.68 (0.55 to 0.81)	OR 0.69 (0.55 to 0.84)	OR 0.64 (0.31 to 1.27)	OR 0.50 (0.32 to 0.78)	OR 0.90 (0.76 to 1.03)	OR 0.74 (0.56 to 0.94)	60 nonvertebral fractures per 1000
	13 fewer per 1000 (5 to 20 fewer)	18 fewer per 1000 (11 to 26 fewer)	18 fewer per 1000 (9 to 26 fewer)	21 fewer per 1000 (41 fewer to 15 more)	29 fewer per 1000 (13 to 40 fewer)	6 fewer per 1000 (14 fewer to 2 more)	15 fewer per 1000 (3 to 25 more)	
Hip fractures - 139 647 participants, 40 trials; Vertebral fractures – 126 423 participants, 67 trials; Nonvertebral fractures – 136 557 participants, 66 trials.				Based on 59,209 participants, 30 trials.	Hip fractures - 139 647 participants, 40 trials; Vertebral fractures – 126 423 participants, 67 trials; Nonvertebral fractures – 136 557 participants, 66 trials.			
⊕⊕⊕⊖ moderate From network meta-analysis with trials with risk of bias; population primarily community (Murad 2012)				⊕⊕⊕⊖ moderate From network meta-analysis with trials with risk of bias; population primarily community (Hopkins 2011)	⊕⊕⊕⊖ moderate From network meta-analysis with trials with risk of bias; population primarily community (Murad 2012)			

Outcomes	Effects and Quality of the Evidence								
	Bisphosphonates (primarily with at least 500 mg calcium, and with/without vitamin D)				Teriparatide (with calcium and vitamin D)	Raloxifene (with/without calcium and vitamin D)	Denosumab (with calcium and vitamin D)	No drug therapy with calcium and vitamin D	
	Alendronate	Risedronate	Zoledronate	Etidronate					
Mortality	Bisphosphonates only RR 0.91 (0.80 to 1.03) 10 fewer per 1000 (22 fewer to 3 more) Based on 32 880 participants, 8 trials. ⊕⊕⊕⊖ moderate Indirect - community population; some risk of bias (Bolland 2010)				Not reported	Not reported	RR 0.90 (0.80 to 1.00) 10 fewer per 1000 (21 fewer to 0) Based on 15324 participants, 2 trials ⊕⊕⊕⊖ moderate Some risk of bias; Indirect - community population at risk coronary disease (Grady 2010)	RR 0.78 (0.57 to 1.06) 23 fewer per 1000 (46 fewer to 6 more) Based on 7808 participants, 1 trial ⊕⊕⊕⊖ low Imprecision; indirect - community population; some risk of bias (Bolland 2010)	110 deaths per 1000 (No calcium and Vitamin D - 120 deaths per 1000)
Quality of life (including pain)	No significant difference with zoledronate Based on 599 participants, 1 trial ⊕⊕⊕⊖ low Imprecision; Risk of bias; indirect population (Hadji 2012)	Not reported	No meaningful differences with placebo at 1,2,3 years Based on 1434/7765 participants, 1 trial ⊕⊕⊕⊖ low Imprecision; Risk of bias; indirect population (Sambrook 2011)	Not reported	RR 0.60 (0.48 to 0.75) 52 fewer per 1000 (62 to 33 fewer) Based on 2 670 participants, 5 trials ⊕⊕⊕⊖ low Some risk of bias; Indirect – community population, imprecision (Nevitt 2006)	No significant difference Based on 129 participants, 1 trial ⊕⊕⊕⊖ low Risk of bias; imprecision; indirect population (Jacobsen 2012)	No significant difference Based on 7808 participants, 1 trial ⊕⊕⊕⊖ moderate Some risk of bias; Indirect - community population (Silverman 2012)	Back pain 130/1000 per 1000	
Osteonecrosis of the Jaw	<1/100 000 (IOF); <1/10 000 (Rizzoli 2011)				Not reported	Not reported	<1/10 000 (Rizzoli 2011)		
Atypical fracture/delayed fracture healing	6/10 000 (Rizzoli 2011)				Not reported	Not reported	Not reported	3/10 000 (no Calcium and Vitamin D)	

Outcomes	Alendronate	Risedronate	Zoledronate	Etidronate	Teriparatide	Raloxifene	Denosumab	No drug therapy with calcium and Vitamin D
Venous thrombo-embolism	1 trial reported 1/93 events vs no events in control *	Not reported	Not reported	Not reported	Not reported	OR 1.63 (1.36 to 1.98)* 12 more per 1000 (7 to 19 more)	Not reported	20 events per 1000 *
Severe infections	Not reported				Not reported	Not reported	RR 1.26 * (1.01 to 1.57) 8 more per 1000 (0 to 18 more) >1/100 (Rizzoli 2011: RCT only)	32 infections per 1000 *
Cardiovascular events	Serious Atrial Fibrillation Bisphosphonates OR 1.59 (0.61 to 3.75) 54 more per 1000 (40 fewer to 207 more) (Mak 2009)				Not reported	Major event OR 1.2 * (1.11 to 1.29) 19 more per 1000 (11 to 28 more)	Not reported	110 major cardiovascular event per 1000
Serious gastrointestinal events	OR 1.09 * (0.89 to 1.33) 1 more per 1000 (2 fewer to 5 more)	OR 0.94 * (0.75 to 1.19) 1 less per 1000 (4 fewer to 3 more)	Not reported	Similar effect to placebo (Wells 2008)	Not reported	No significant difference*	Not reported	16 serious GI events per 1000 *
Musculoskeletal (arthritis, arthralgia, myalgia)	OR 1.06 * (0.91 to 1.23) 4 more per 1000 (7 fewer to 17 more) >1/100 (Rizzoli 2011)	OR 0.77 * (0.45 to 1.32) 17 fewer per 1000 (42 fewer to 23 more) >1/100 (Rizzoli 2011)	OR 3.36 * (2.96 to 3.82) 146 more per 1000 (125 to 169 more) >1/10 (Rizzoli 2011)	Not reported	Not reported	OR 1.42 * (1.21 to 1.67) 30 more per 1000 (15 to 47 more) >1/100 (Rizzoli 2011)	Not reported	80 events per 1000 *
Based on pharmacovigilance and case series (Rizzoli 2011); and/or systematic reviews and meta-analyses from AHRQ 2012 (* when indicated)⊕⊕⊕⊖ moderate to ⊕⊕⊖⊖ low Due to risk of bias; Indirect - community population; short term follow-up with Denosumab								

Note: The absolute effects of Vitamin D with calcium were added to the effect of No drug therapy and then multiplied by the relative risk for each drug to calculate the absolute effect of each drug.

A5.4 Resources used to inform the recommendations

Systematic reviews and reviews

- Agency for Healthcare Research and Quality: Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report. Comparative Effectiveness Review Number 53. March 2012. Available at <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1006>. Accessed 29 August 2013.
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Randomised controlled trials

- Hadji P, Ziller V, Gamerdinger D, Spieler W, Articus K, Baier M, Moericke R, Kann PH. Quality of life and health status with zoledronic acid and generic alendronate--a secondary analysis of the Rapid Onset and Sustained Efficacy (ROSE) study in postmenopausal women with low bone mass. *Osteoporos Int.* 2012 Jul;23(7):2043-51.
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A6 Hip Protectors

Should hip protectors be recommended for elderly in long term care to prevent fractures?

A6.1 Recommendations, Remarks, and Evidence Summary

RECOMMENDATION

For residents who are mobile and at HIGH RISK of FRACTURES, we recommend hip protectors (strong recommendation, moderate quality evidence). For residents who are *not* at high risk of fracture but are mobile, we suggest hip protectors depending on resources and their values and preferences (conditional recommendation, moderate quality evidence).

Remarks: These recommendations place a high value on avoiding the serious consequences of hip fractures including death, pain and loss of mobility, in mobile residents. A lower value was placed on the cost or burden to an individual or to the long-term care home's resources. Due to the small reductions in hip fractures, elderly not at high risk of hip fractures may choose alternative options to prevent fractures. It is recognised that adherence to wearing hip protectors may be challenging and therefore strategies to improve adherence may be needed. This recommendation applies to hard or soft hip protectors and may depend on preference.

Evidence summary: Moderate quality evidence from systematic reviews showed a relative risk reduction in hip fractures of 18% (95% CI 0 to 33%) in the elderly wearing hip protectors in institutional settings (Santesso 2014). Over 1 year, there would be 4 fewer hip fractures (95% CI 1 to 7) per 1000 elderly wearing hip protectors, and in the higher risk elderly 13/1000 fewer (95% CI 2 to 22). However, there was 1 more pelvic fracture (95% CI 0 to 4) in elderly not at high risk, and 8 more (95% CI 5 to 38) in high risk elderly. Moderate evidence also showed that there is probably little or no difference in falls or adverse events requiring medical attention, and that minor adverse events, such as skin irritation, occurred in less than 2% of people wearing hip protectors (soft or hard). The effect on quality of life and mortality is uncertain; and data for pain, anxiety, mobility and performance of activities of daily living is not available. Adherence to hip protector use varied across studies from 24 to 80%. The impact of adherence on the effects of hip protectors is unclear, but the effects found may represent the true effects when implemented.

A6.2 Question, Evidence to Recommendations Table for HIP Protectors

QUESTION

Population	Elderly in long term care*
Intervention	Hip protectors (soft or hard) to prevent fractures
Comparison	No hip protectors
Outcomes	Hip fractures, vertebral and other fractures, pain, agitation, mobility, independence for activities of daily living (qol), mortality, resource use or costs, acceptability, severe adverse events, minor adverse events requiring medical attention

* Long term care can refer to the following depending on country: Long Term Care Home, Retirement Home, Nursing Home, Skilled Nursing Facility, Care Home, Care Home (with Nursing), Residential Aged Care Facility, and Hostels.

Decision domain:	Explanation	Summary of reason for judgement	Judgement
Quality of evidence (QoE) <i>Is there high or moderate quality evidence?</i> The higher the quality of evidence, the more likely is a strong recommendation	QoE for benefits: Moderate QoE for harms: Moderate QoE for resource use: Moderate Key reasons for downgrading the evidence: Imprecision and risk of bias		Yes No X <input type="checkbox"/>
Balance of benefits versus harms and burdens <i>Are you confident that the benefits outweigh the harms and burden or vice versa?</i> The larger the difference between the benefits and harms and the certainty around that difference, the more likely is a strong recommendation. The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional recommendation.	Overall risk groups: Probably reduces hip fractures by 4/1000 (0 to -7) May increase pelvic fractures by 1/1000 (0 to 4) High risk groups: Probably reduces hip fractures by 11/1000 (0 to -20) May increase pelvic fractures by 8/1000 (-3 to 30) All groups: Probably little or no difference in falls or adverse events requiring medical attention; Uncertain effect on quality of life; Uncertain effect on mortality; No data for pain, anxiety, mobility and ADL There may be little or no difference between soft and hard hip protectors.	In the elderly at risk of hip fractures, there is a small net benefit of hip protectors. In the elderly at high risk of hip fractures, there is a large net benefit of hip protectors.	Overall risk Yes No <input type="checkbox"/> X High risk Yes No X <input type="checkbox"/>
Values and preferences <i>Are you confident about the assumed or identified relative values and are they similar across the target population?</i> The more certainty or similarity in values and preferences, the more likely a strong recommendation.	Systematic review of studies in long term care reported adherence between 24 to 80% (Gillespie 2010). It is not known if related to type of hip protectors. Better adherence in people with history of falls or fracture and hypertension, and in homes with more falls and fractures, and with fewer people wearing hip protectors. Lower adherence in people with arthritis of lower limbs. Unclear association with mobility, incontinence, cognitive impairment (Cryer 2008; Zimmerman 2010). Some qualitative research reports people place high value on avoiding pain with hip fracture/loss of mobility. Downstream consequences of hip fractures: 50-80% greater mortality; 65% lose mobility; meaningful loss in quality of life.	Perspective taken: Patient Assumption that adherence represents value placed on wearing hip protectors which was not similar across people. Although adherence may be greater in those at higher risk. Avoiding a hip fracture and pain was highly valued.	Yes No <input type="checkbox"/> X

<p>Resource implications <i>Are the resources worth the expected net benefit from following the recommendation?</i></p> <p>The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention.</p>	<p><i>Difference in annual cost per 1000 with hip protector</i></p> <table border="1"> <thead> <tr> <th></th> <th><i>Overall risk</i></th> <th><i>High risk</i></th> </tr> </thead> <tbody> <tr> <td><i>Three soft hip protectors (\$240)</i></td> <td><i>+\$240 000</i></td> <td><i>+\$240 000</i></td> </tr> <tr> <td><i>Hip fracture</i></td> <td><i>-\$144 000</i></td> <td><i>-\$396 000</i></td> </tr> <tr> <td><i>Pelvic fracture*</i></td> <td><i>+\$11 000</i></td> <td><i>+\$88 000</i></td> </tr> <tr> <td><i>TOTAL</i></td> <td><i>+\$107 000</i></td> <td><i>-\$68 000</i></td> </tr> </tbody> </table>			<i>Overall risk</i>	<i>High risk</i>	<i>Three soft hip protectors (\$240)</i>	<i>+\$240 000</i>	<i>+\$240 000</i>	<i>Hip fracture</i>	<i>-\$144 000</i>	<i>-\$396 000</i>	<i>Pelvic fracture*</i>	<i>+\$11 000</i>	<i>+\$88 000</i>	<i>TOTAL</i>	<i>+\$107 000</i>	<i>-\$68 000</i>	<p>Costs were estimated from the cost to an individual in the community. Hip protectors are generally accessible in institutions and community. Costs/resources do not vary widely across settings [cost for staff in institutions not considered].</p> <p>The benefits of the hip protectors do not outweigh the costs in the elderly at risk of hip fractures. However, the benefits do outweigh the costs in elderly at high risk</p>	<p>Overall risk Yes No <input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>High risk Yes No <input checked="" type="checkbox"/> <input type="checkbox"/></p>
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BASELINE RISKS AND COSTS

See A3. page 9 &10 for: a) estimates regarding the risk of fractures among residents at high risk of fracture and among all older LTC residents and b) estimates regarding the costs associated with treating fractures.

A6.3 Evidence Profile

Hip protectors compared to no hip protectors to prevent fractures for elderly in long term care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects <u>per year</u>	
				Risk with No hip protectors	Risk difference with Hip protectors (95% CI)
Number of elderly with a hip fracture	10688 (13 studies) up to 24 months	⊕⊕⊕⊖ MODERATE ^{1,2} due to risk of bias, imprecision	Risk Ratio 0.82 (0.67 to 1.00)	Overall risk	
				20 hip fractures per 1000	4 fewer hip fracture per 1000 (from 0 to 7 fewer)
				High risk	
				60 hip fractures per 1000	11 fewer hip fractures per 1000 (from 0 to 20 fewer)
Number of elderly with a pelvic fracture	7273 (6 studies) up to 24 months	⊕⊕⊕⊖ MODERATE ^{1,2} due to risk of bias, imprecision	Risk Ratio 1.56 (0.77 to 3.13)	Overall risk	
				2 pelvic fractures per 1000	1 more pelvic fracture per 1000 (from 0 to 4 more)
				High risk	
				14 pelvic fractures per 1000	8 more pelvic fractures per 1000 (from 3 fewer to 30 more)
Minor adverse events requiring medical attention	11573 (14 studies) up to 24 months	⊕⊕⊕⊖ MODERATE ¹ due to risk of bias	See comment	See comment	No studies reported adverse events requiring medical attention. 3/14 studies reported ~2% or fewer people with skin irritation.
Falls per elderly per year	4770 (11 studies) up to 24 months	⊕⊕⊕⊖ MODERATE ¹ due to risk of bias	Rate Ratio 1.00 (0.86 to 1.17)	Overall risk	
				3 falls per person per year	0 fewer falls per person per year (from 0 fewer to 0 more)
Quality of life EuroQol -5D (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Scale from: 0 to 1.0 (optimal health).	235 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW ^{3,4} due to risk of bias, imprecision	-	The mean quality of life ranged from 0.70 to 0.75	The mean quality of life was 0.13 lower (0.23 to 0.03 lower)
Adherence to hip protectors	10688 (13 studies) up to 24 months	⊕⊕⊕⊖ LOW ^{4,5} due to risk of bias, inconsistency	See comment	See comment	Ranged from 24 to 80%.
Mortality	1749 (4 studies) 12 to 24 months	⊕⊖⊖⊖ VERY LOW ^{1,6} due to risk of bias, imprecision	Risk Ratio 0.96 (0.84 to 1.09)	120 deaths per 1000	5 fewer deaths per 1000 (from 19 fewer to 11 more)

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Unclear or no blinding of participants, investigators and outcome assessors, and loss to follow-up ranging from 0 to 56%.

² Imprecision related to absolute events with wide confidence intervals close to no beneficial effect.

³ Results imprecise as confidence intervals around absolute effects include potential for important benefit or very small/no effect.

⁴ Unclear blinding of participants, investigators and assessors, and baseline score was significantly lower in intervention group.

⁵ Inconsistency due to wide range of adherence and adherence measured/reported in different ways.

⁶ Unclear or no blinding of participants, investigators and outcome assessors, loss to follow-up, and high risk of bias due to outcome reporting bias.

Soft hip protectors compared to hard hip protectors for elderly living in long term care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Hard hip protectors	Risk difference with Soft hip protectors (95% CI)
Hip fractures per person per year	1236 (1 study) up to 12 months	⊕⊕⊖⊖ LOW ^{1,2} due to risk of bias and imprecision	Rate Ratio 0.73 (0.45 to 1.17)	0.06 hip fractures per person per year	0.02 fewer hip fractures per person per year (from 0.03 fewer to 0.01 more)

¹ There are few events in the studies resulting in imprecision. In addition, subgroup analysis of randomised controlled studies of soft or hard hip protectors versus no hip protector showed no significant difference between subgroups.

² Unclear blinding of participants, investigators and assessors.

A6.4 Resources used to inform the recommendations

Systematic reviews and reviews

- Cryer C, Knox A, Stevenson E. Factors associated with hip protector adherence among older people in residential care. *Inj Prev.* 2008 Feb;14(1):24-9.
- Santesso N, Carrasco-Labra A, Brignardello-Petersen R. Hip protectors for preventing hip fractures in older people. *Cochrane Database of Systematic Reviews* (in press).
- Sawka A M, Boulos P , Beattie K , Thabane L , Papaioannou A , Gafni A , Cranney A , Zytaruk N , Hanley D A and Adachi J D. Do hip protectors decrease the risk of hip fracture in institutional and community-dwelling elderly: a systematic review and meta-analysis of randomized controlled trials. *Osteoporosis International*, 2005, 16(12), 1461-1474.

Randomised controlled trials

- Bentzen H, Bergland A, Forsén L. Risk of hip fractures in soft protected, hard protected, and unprotected falls. *Inj Prev.* 2008 Oct;14(5):306-10
- Kiel DP, Magaziner J, Zimmerman S, Ball L, Barton BA, Brown KM, et al Efficacy of a hip protector to prevent hip fracture in nursing home residents: the HIP PRO randomized controlled trial. *JAMA* 2007; 298(4):413-22.
- Schaafsma FG, Kurrle SE, Quine S, Lockwood K, Cameron ID. Wearing hip protectors does not reduce health-related quality of life in older people. *Age Ageing.* 2012 Jan;41(1):121-5.
- Zimmerman S, Magaziner J, Birge SJ, Barton BA, Kronsberg SS, Kiel DP. Adherence to hip protectors and implications for U.S. long-term care settings. *J Am Med Dir Assoc.* 2010 Feb;11(2):106-15.

A7 Exercise

Should exercise be recommended for elderly in long term care to prevent fractures?

A7.1 Recommendations, Remarks and Evidence Summary

RECOMMENDATION

For residents NOT at high risk of fractures, we suggest balance, strength and functional training exercises to prevent falls. (conditional recommendation, moderate quality evidence)

Remarks: This recommendation places a high value on the probable small reduction in falls, as falls may lead to serious injuries. It also places a high value on the other benefits that exercise could provide and places a lower value on the uncertain costs to implement exercise interventions in long-term care.

For residents at HIGH RISK of FRACTURES, we suggest balance, strength and functional training exercises only when part of a multifactorial intervention to prevent falls. (conditional recommendation, low quality evidence)

Remarks: This recommendation places a high value on avoiding the small increase in falls which may occur among individuals at high risk of falls who participate in exercises, such as balance, strength and functional training. Some elderly may value exercising despite the potential risk of falls. When exercise is provided, it should be provided as part of a multifactorial intervention to prevent falls (including medication review (see the Beers Criteria), assessment of environmental hazards, or use of assistive devices), or with other interventions to prevent fractures (including vitamin D and calcium, hip protectors, and pharmacological therapies).

Evidence Summary: This recommendation is based on systematically reviewed evidence that is moderate to low quality (Cameron 2012). The review provided subgroup analyses in the elderly in high level care and intermediate care facilities which was used to inform the recommendations for those at high risk and not at high risk of fractures (respectively). Most studies did not measure fractures, quality of life, mobility or pain. Instead, the risk of falls was used to inform this recommendation. Costs were not reviewed.

Exercise in elderly residents at high risk of fractures may increase the number of falls (87 more per 1000 elderly, 95% CI -21 to 237), and may increase the number of elderly falling (85/1000 more, 95% CI -20 to 210). In elderly residents *not* at high risk of fractures, exercise probably reduces the number of falls (60 fewer per 1000 elderly, 95% CI -129 to 39), and probably results in a small reduction in the number of elderly falling (20/1000 fewer, 95% CI -115 to 105). These results were from studies that evaluated balance (such as Tai Chi), strength and functional training. One study measured hip fractures, but the results are very uncertain due to very few events. In a systematic review of exercise as part of a multifactorial intervention to prevent falls, it was shown that the multifactorial intervention may reduce falls (660 fewer falls per 1000

elderly per year, 95% CI -1000 to 120), reduce the number of elderly who fall (55/1000 fewer, 95% CI -115 to 10) and hip fractures (10 fewer/1000, 95% CI -14 to 1) (Cameron 2012).

A7.2 Question, Evidence to Recommendations Table for Exercise
QUESTION

Population	Elderly in long term care*
Intervention	Exercises (any type) to prevent falls
Comparison	Usual care
Outcomes	Falls, fractures

* Long term facilities can refer to the following depending on country: Long Term Care Home, Retirement Home, Nursing Home, Skilled Nursing Facility, Care Home, Care Home (with Nursing), Residential Aged Care Facility, and Hostels.

Decision domain:	Explanation	Summary of reason for judgement	Judgement
<p>Quality of evidence (QoE) <i>Is there high or moderate quality evidence?</i> The higher the quality of evidence, the more likely is a strong recommendation</p>	<p>QoE for benefits: Moderate to low Key reasons for downgrading the evidence: Risk of bias and unexplained heterogeneity (data for elderly in high care facilities applied to elderly at high risk of fractures)</p> <p>There was no data for outcomes such as quality of life, mobility, pain, etc.</p>		<p>Yes No <input type="checkbox"/> <input checked="" type="checkbox"/></p>
<p>Balance of benefits versus harms and burdens <i>Are you confident that the benefits outweigh the harms and burden or vice versa?</i> The larger the difference between the benefits and harms and the certainty around that difference, the more likely is a strong recommendation. The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional/weak recommendation.</p>	<p>For elderly at high risk of fractures, exercise: -may increase number of falls, 87 more falls per 1000 elderly (-21 to +237) -may increase number of elderly falling, 85/1000 more (-20 to +210)</p> <p>For elderly not at high risk of fractures, exercise: -probably reduces number of falls, 60 fewer falls per 1000 elderly (-129 to +39) - probably small reduction in number of elderly falling, 20/1000 fewer (-115 to +105)</p> <p>The effect on hip fractures is uncertain. Other harms were not reported The effect of different types of exercise is uncertain due to lack of enough data for analysis.</p> <p>Exercise as part of a multifactorial intervention may reduce falls (660 fewer falls per 1000 elderly per year, -1000 to 120), reduce the number of elderly who fall (55/1000 fewer will fall per year, -115 to 10) and reduce hip fractures (10 fewer per 1000 elderly per year, -14 to 1).</p>	<p>The harms may outweigh the benefits in elderly at high risk of fractures. However, when exercise is part of a multifactorial intervention benefits slightly outweigh harms.</p> <p>The benefits slightly outweigh harms in elderly not at high risk of fractures.</p>	<p>High risk Yes No <input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Not at high risk Yes No <input checked="" type="checkbox"/> <input type="checkbox"/></p>
<p>Values and preferences <i>Are you confident about the assumed or identified relative values and are they similar across the target population?</i> The more certainty or similarity in values and preferences, the more likely a strong recommendation.</p>	<p>One-third of all falls may result in an injury and every fifth injurious fall may result in treatment outside the patient's own setting (Nurmi 2002)</p> <p>Consequences hip fracture: LTC with fracture 50-80% increased mortality risk over LTC with no fracture; 65% lose mobility; meaningful loss in quality of life.</p>	<p>High value placed on avoiding a fall which may lead to serious injuries, resident fear of falling, and burden to facility staff.</p>	<p>Yes No <input checked="" type="checkbox"/> <input type="checkbox"/></p>

	<p>The panel felt that a high value should be placed on increased fear of falling in residents and likely the additional burden to staff when residents fall.</p>		
<p>Resource implications <i>Are the resources worth the expected net benefit from following the recommendation?</i></p> <p>The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention.</p>	<p>Access to physiotherapy, physiotherapists and assistants, kinesiologists is currently available in long term care with some variability across provinces.</p> <p>There is little research about the costs and resources required to provide specific exercise interventions in long term care.</p>	<p>Resources likely worth the benefits in elderly at low risk</p>	<p>Yes No X <input type="checkbox"/></p>

A7.3 Evidence Profile, Meta-Analyses regarding Exercise

Exercise compared to Usual Care in the elderly at HIGH risk of fractures in long term care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects at 1 year	
				Risk with Usual Care	Risk difference with Exercise (95% CI)
Number of falls per 1000 elderly per year	625 (4 studies)	⊕⊕⊕⊖ LOW ^{1,2,3} due to risk of bias, imprecision	Rate Ratio 1.29 (0.93 to 1.79)	300 falls per 1000 elderly	87 more falls per 1000 elderly (from 21 fewer to 237 more)
Number of elderly who fall at least once in one year	609 (3 studies)	⊕⊕⊕⊖ LOW ^{1,3} due to risk of bias, imprecision	RR 1.17 (0.96 to 1.42)	500 elderly fall per 1000	85 more elderly fall per 1000 (from 20 fewer to 210 more)
Number of elderly who have a hip fracture in one year	183 (1 study)	⊕⊖⊖⊖ VERY LOW ^{1,3} due to risk of bias, imprecision	RR 0.16 (0.01 to 2.81)	-	-
Other benefits or harms	Not measured				

Exercise compared to Usual Care in the elderly NOT AT HIGH risk of fractures in long term care

Number of falls per 1000 elderly per year	1229 (4 studies)	⊕⊕⊕⊖ MODERATE ^{1,2} due to risk of bias	Rate Ratio 0.80 (0.57 to 1.13)	300 falls per 1000 elderly	60 fewer falls per 1000 elderly (from 129 fewer to 39 more)
Number of elderly who fall at least once in one year	1278 (5 studies)	⊕⊕⊕⊖ MODERATE ¹ due to risk of bias	RR 0.96 (0.77 to 1.21)	500 elderly fall per 1000	20 fewer elderly fall per 1000 (from 115 fewer to 105 more)
Number of elderly who have a hip fracture in one year	183 (1 study)	⊕⊖⊖⊖ VERY LOW ^{1,3} due to risk of bias, imprecision	RR 0.16 (0.01 to 2.81)	-	-
Other benefits or harms	Not measured				

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Outcome assessors were not blinded to intervention in studies and unclear or no allocation concealment or sequence generation.

² Some heterogeneity among studies but considered with risk of bias to downgrade quality of evidence.

³ Results imprecise due to few participants in analysis.

A7.4 Resources used to inform the recommendations

- Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, Kerse N. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev.* 2012 Dec 12;12:CD005465. doi: 10.1002/14651858.CD005465.pub3.

Outcomes post-hip fracture and falls

- Beupre LA, Jones CA, Johnston DW, Wilson DM, Majumdar SR. Recovery of function following a hip fracture in geriatric ambulatory persons living in nursing homes: prospective cohort study. *J Am Geriatr Soc.* 2012 Jul;60(7):1268-73.
- Nikitovic M, Wodchis WP, Krahn MD, Cadarette SM. Direct health-care costs attributed to hip fractures among seniors: a matched cohort study. *Osteoporos Int.* 2012 Jun 27.
- Nurmi I, Lüthje P. Incidence and costs of falls and fall injuries among elderly in institutional care. *Scand J Prim Health Care.* 2002 Jun;20(2):118-22.

A8. Multifactorial Interventions

Should multifactorial interventions to prevent fractures be recommended for elderly in long term care?

A8.1 Recommendations, Remarks and Evidence Summary

RECOMMENDATION

For ALL RESIDENTS, we suggest multifactorial interventions that are individually tailored to reduce the risk of falls and fractures. (conditional recommendation, low quality evidence)

Remarks: Multifactorial interventions are defined as any combination of interventions that are tailored to an individual's risk to reduce falls. These interventions may include medication reviews (see Beers Criteria), assessment of environmental hazards, use of assistive devices, exercise, management of urinary incontinence, and educational interventions directed to staff. This recommendation is conditional due to the low quality evidence for important but small benefits and the unknown and potentially greater costs to implement multifactorial interventions in long term care. A high value was placed on the small reductions in falls that may occur, as falls may lead to serious injuries. We have not suggested which interventions must be part of a multifactorial intervention as it is unclear which combination of strategies provides benefit. It will be important to consider the resident's level of fracture risk and tailor strategies accordingly.

Evidence Summary: The evidence from a systematic review of interventions to prevent falls in older people in care facilities was of low quality due to the risk of bias of the included studies, and moderate to high inconsistency of effects across studies which could not be explained by the level of care, cognition or combination of interventions (Cameron 2012). Most studies did not measure fractures, quality of life, mobility or pain, therefore, the risk of falls was used to inform this recommendation. Overall, there may be 660 fewer falls per 1000 elderly per year (-1000 to 120) , and 55/1000 fewer (95% CI -115 to 10) will fall with multifactorial interventions. There was low quality of evidence for a reduced risk of hip fractures (10/1000 fewer, 95% CI -14 to 1). There were insufficient data to explore the effects of different combinations of interventions, or specific interventions, and their human and financial costs

A 8.2 Question, Evidence to Recommendations Table regarding Multifactorial Interventions

QUESTION

Population	Elderly in long term care *
Intervention	Including more than one intervention tailored to an individual (e.g. environmental, exercises, etc.)
Comparison	Usual care
Outcomes	Falls, fractures

* Long term care can refer to the following depending on country: Long Term Care Home, Retirement Home, Nursing Home, Skilled Nursing Facility, Care Home, Care Home (with Nursing), Residential Aged Care Facility, and Hostels

Decision domain:	Explanation	Summary of reason for judgement	Judgement
<p>Quality of evidence (QoE) <i>Is there high or moderate quality evidence?</i> The higher the quality of evidence, the more likely is a strong recommendation</p>	<p>QoE for benefits: Low Key reasons for downgrading the evidence: Risk of bias and unexplained heterogeneity after exploration of effect by level of care, level of cognition and type of interventions; and imprecision for hip fracture data No data for quality of life, mobility, pain, etc.</p>		<p>Yes No <input type="checkbox"/> <input checked="" type="checkbox"/></p>
<p>Balance of benefits versus harms and burdens <i>Are you confident that the benefits outweigh the harms and burden or vice versa?</i> The larger the difference between the benefits and harms and the certainty around that difference, the more likely is a strong recommendation. The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional recommendation.</p>	<p>With multifactorial interventions, there - May be 660 fewer falls per 1000 (-1000 to 120) elderly per year - May be 55 fewer (-115 to 10) elderly will fall per year - May be 10 fewer hip fractures (-14 to 1) per 1000 elderly per year</p> <p>Harms were not reported and information from observation would suggest no potential for other harms.</p> <p>There was no significant interaction between studies with elderly in high or mixed levels versus intermediate levels of care, or in elderly with higher or lower cognition.</p> <p>The effects of different combinations of interventions is uncertain due to insufficient data.</p> <p>The effects of exercise interventions alone in elderly at high risk of fractures may increase falls and the number of fallers.</p>	<p>The benefits slightly outweigh any harms that may occur.</p>	<p>Yes No <input checked="" type="checkbox"/> <input type="checkbox"/></p>
<p>Values and preferences <i>Are you confident about the assumed or identified relative values and are they similar across the target population?</i> The more certainty or similarity in values and preferences, the more likely a strong recommendation.</p>	<p>One-third of all falls may result in an injury and every fifth injurious fall may result in treatment outside the patient's own setting (Nurmi 2002)</p> <p>Consequences of hip fracture: LTC with fracture 50-80% increased mortality risk over LTC with no fracture; 65% lose mobility; meaningful loss in quality of life.</p>	<p>A high value was placed on the risk of falls which may lead to serious injuries, resident fear of falling, and burden to facility staff.</p>	<p>Yes No <input checked="" type="checkbox"/> <input type="checkbox"/></p>

	<p>The panel felt that a high value should be placed on increased fear of falling in elderly and likely the additional burden to staff when residents fall.</p>		
<p>Resource implications <i>Are the resources worth the expected net benefit from following the recommendation?</i></p> <p>The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention.</p>	<p>The costs of implementation of multifactorial interventions was not determined and there is little to no research about costs.</p> <p>There may be high human and financial costs to implement multifactorial interventions across all residents in long term care.</p> <p>The costs of different interventions will also vary.</p>	<p>The costs of the interventions may outweigh the serious consequences and costs of fractures; but will vary across settings</p> <p>A low value has been placed on costs of interventions in long term care</p>	<p>Yes No <input type="checkbox"/> X</p>

A8.3 Evidence Profile regarding Multifactorial Interventions

Multifactorial interventions compared to Usual Care for elderly in long term care					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects at 1 year	
				Risk with Usual Care	Risk difference with Multimodal interventions (95% CI)
Number of falls per 1000 elderly per year	2876 (7 studies)	⊕⊕⊖⊖ LOW ^{1,2,3} due to risk of bias, inconsistency	Rate Ratio 0.78 (0.59 to 1.04) ¹	Moderate ⁴	
				3000 falls per 1000 elderly	660 fewer falls per 1000 elderly (from 1000 fewer to 120 more)
Number of elderly who fall at least once in one year	2632 (7 studies)	⊕⊕⊖⊖ LOW ² due to risk of bias, inconsistency	RR 0.89 (0.77 to 1.02) ¹	Moderate ⁴	
				500 elderly fall per 1000	55 fewer elderly fall per 1000 (from 115 fewer to 10 more)
Number of people who sustained a hip fracture in one year	1822 (4 studies)	⊕⊕⊖⊖ LOW ^{2,5} due to risk of bias, imprecision	RR 0.56 (0.30 to 1.03) ¹	Moderate	
				20 per 1000 elderly	10 fewer per 1000 elderly (from 14 fewer to 1 more)
Other benefits or harms	Not measured				

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Outcome assessors were not blinded to intervention in studies and unclear or no allocation concealment or sequence generation.

² Moderate to high heterogeneity among studies which could not be explained by subgroup analyses by level of care, level of cognition or mix of interventions (e.g. including exercise vs not including exercise).

³ There was no significant interaction in studies between people in high or mixed levels versus intermediate levels of care, or in people with higher or lower cognition.

⁴ Baseline risk with usual care is median across included studies.

⁵ Few hip fractures occurred in studies and therefore results are imprecise.

A8.4 Resources used to inform the recommendations

- Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, Kerse N. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012 Dec 12;12:CD005465

Outcomes post-hip fracture and falls

- Beaupre LA, Jones CA, Johnston DW, Wilson DM, Majumdar SR. Recovery of function following a hip fracture in geriatric ambulatory persons living in nursing homes: prospective cohort study. J Am Geriatr Soc. 2012 Jul;60(7):1268-73.
- Nikitovic M, Wodchis WP, Krahn MD, Cadarette SM. Direct health-care costs attributed to hip fractures among seniors: a matched cohort study. Osteoporos Int. 2012 Jun 27.
- Nurmi I, Lüthje P. Incidence and costs of falls and fall injuries among elderly in institutional care. Scand J Prim Health Care. 2002 Jun;20(2):118-22.