APPENDIX 1 (as submitted by the authors):

Recommendations for Preventing Fractures in Long-term Care

Supplementary Materials

Appendix to: Papaioannou A, Santesso N, Morin SN, et al. Recommendations for preventing fracture in long-term care. *CMAJ* 2015. DOI: 10.1503/cmaj.141331.

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Development of the Recommendations

A1. Methods

The methods to develop fracture prevention recommendations for Long-term Care (LTC) followed the Grading of Recommendations Assessment, Evaluation and Development (GRADE) approach to guideline development (Guyatt 2008; Guyatt 2011) (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, librarians, Grade methodologists and epidemiologists. See A2. page 6 for participants and organizations represented. A selected smaller group, the Investigator Group of 12 members, and the Methods Group 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 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.

To describe the effects of the interventions, we used consistent wording in the Summary of the evidence for each recommendation. The wording is based on work to translate the effects of interventions into a plain language (Glenton 2010). We incorporated the level of evidence or confidence in the effect and the magnitude of the effect to determine the wording (see Table 1).

TABLE 1. Wording for the effects of the interventions

Level of evidence	Important benefit/harm	Less important benefit/harm	No important benefit/harm or null effect
High	improves*	improves slightly	little or no difference
Moderate	probably improves may likely improve	probably improves slightly may likely improve slightly	probably little or no difference may likely have little or no difference
Low	evidence suggests improvement may improve	evidence suggests slight improvement may improve slightly	evidence suggests little or no difference may have little or no difference
Very low	We are uncertain whether [intervention] improves [outcome]		

**other words can be used to communicate the direction of effect (e.g. reduces or increases)*

Development of the Recommendations - On January 11th 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 2). Strong recommendations are worded as 'we recommend' and conditional as 'we suggest'.

TABLE 2. 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.	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.	Clinicians recognize that different choices will be appropriate for each individual patient and that clinicians must help each individual arrive at a management decision consistent with his or her values and preferences.

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A2. Participants and Organizations represented in the Panel

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Dr. Nancy Santesso	McMaster University / GRADE working group
Dr. JD. Adachi	McMaster University
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Dr. Angela Cheung	University of Toronto / Chair, Osteoporosis Canada, Scientific Advisory Council
Dr. Richard Crilly	University of Western Ontario
Linda Dacres	Nurse Practitioners' Association of Ontario (NPAO)
Dr. Sid Feldman	Ontario Long Term Care Physicians (OLTCP) / Ontario College of Family Physicians (OCFP)
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
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Dr. Angela Juby	University of Alberta / Canadian Geriatrics Society
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Dr. Courtney Kennedy	McMaster University
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Dr. Amy Maher	McMaster University
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A3. Estimates of Baseline Risks in the 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; estimated increased relative risk of 3.0 in people with previous higher risk of fractures 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, attributable 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 older people in long-term care?

A4.1 Recommendations, Remarks, and Evidence Summary

RECOMMENDATIONS

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 reductions in fractures, mortality and falls and a lower value on the resources in long-term care that are required to implement interventions to ensure adequate dietary intake of calcium. This recommendation is based on evidence evaluating the effects of calcium supplements, which was used as direct evidence for dietary intake; however, dietary interventions do not have the adverse effects of supplements. For people older than 70 years, the recommended dietary allowance for calcium is 1200 mg daily (3 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 carers') 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 in mortality that can be achieved with calcium supplementation. It places a lower value on the small increased risk of gastrointestinal adverse effects that 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 benefit of calcium supplementation, and adverse effects of supplementation, such as gastrointestinal and renal adverse effects, may occur. For residents who value avoiding these adverse effects, supplementation may not be a desirable option. These recommendations apply to supplementation with any calcium compound, including calcium carbonate or citrate. The recommendation to limit supplementation to 500 mg was based on the

uncertainty about harms of calcium supplementation in studies of community-dwelling individuals who received calcium supplementation of 1000 mg or more daily. The benefits of calcium supplementation are closely linked to adequate vitamin D intake.

RECOMMENDATIONS

Vitamin D

For residents at HIGH RISK of FRACTURES, we recommend daily supplements of 800 IU to 2000 IU vitamin D_3 (strong recommendation, moderate quality evidence).
For residents NOT at high RISK of fractures, we suggest daily supplements of 800 IU to 2000 IU vitamin D_3 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 reductions in hip fractures, mortality and falls and a lower value on the resources in long-term care that are required to provide vitamin D supplementation. The recommendation for residents not at high risk also places a high value on reduction in falls, as they may lead to serious injuries, fear of falling and burden to staff in long-term care; however, there is some uncertainty about a reduction in falls and little to no reduction in fractures with vitamin D supplementation in this group. These recommendations apply to supplementation with D3, as this form may be more accessible because of its lower cost relative to D2. A dose of about 800 IU reduced fractures in people with normal or low 25-hydroxyvitamin D levels and also increased 25-hydroxyvitamin D levels to normal in those with 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 older than 70 years is 800 IU daily, and the tolerable upper intake level is up to 4000 IU.

Evidence summary: Overall there was moderate quality evidence for benefits and low to very low quality evidence for harms of calcium and vitamin D. 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 fewer hip fractures per 1000 (95% CI, 5 to 24 fewer); for residents not at high risk 5 fewer hip fractures per 1000 (95% CI, 2 to 8 fewer); and for all residents, 7 fewer deaths per 1000 (95% CI, 1 to 14 fewer).

We found vitamin D and calcium supplementation likely has little or no effect on vertebral fractures with only 2 fewer vertebral fractures per 1000 (95% CI, 44 fewer to 61 more). The effect is similar with vitamin D only, but a reduction may be likely with calcium only (49 fewer per 1000: 95% CI, 99 fewer to 19 more)(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 2012), quality of life (Grant 2005) or muscle strength (Muir 2011).

The data for falls were not precise (wide confidence intervals including the possibility for benefit, no effect and harm) and the effects were not consistent when the rate or risk of falls was measured (Cameron 2012; Gillespie 2012; Murad 2011; Reid 2006). However, vitamin D and calcium, or vitamin D alone may reduce falls. This is important because 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 performance in relation to calcium and vitamin D.

With respect to minor and major adverse events, vitamin D or calcium supplements probably increase mild or serious gastrointestinal events to a similar extent, approximately 8 per 1000 more (95% CI, 0 to 17 more) (Avenell 2009). Gastrointestinal symptoms or difficulties taking calcium tablets may contribute to poor adherence (Grant 2005; Reid 2006). The evidence suggests slightly more cases of hypercalcaemia (5 more per 1,000: 95% CI, 1 fewer to 18 more) and renal insufficiency or calculi (3 more cases per 1000: 95% CI, 0 to 6 more) with vitamin D (D_2 or D_3) with calcium (Avenell 2009). The evidence for greater myocardial infarctions with supplementation of calcium ≥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 rates of fractures or falls by type of vitamin D (D_3 or D_2) (Avenell 2009; Levis 2012; Murad 2011); that 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 monthly or annual doses (Bischoff-Ferrari 2012; Bischoff-Ferrari 2009). Analyses did find that vitamin D may have greater effects in 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 daily over several months can increase serum vitamin D levels to ‘normal’ levels in people with initial vitamin D deficiency (e.g. ≤ 25 nmol/L).

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

QUESTION

Population	Older people 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
Quality of evidence (QoE) *Is there high or moderate quality evidence?* The higher the quality of evidence, the more likely is a strong recommendation	**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.		Yes ☐ No X
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burden or vice versa?* 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.	**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. There may be little or no difference on fractures or falls by type of vitamin D (D_3 or D_2) (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 months can increase serum vitamin D levels to 'normal' levels in	In high risk older persons, benefits of vitamin D with calcium slightly outweigh harms (little to no adverse events, such as GI and renal, and the uncertain risk of myocardial infarctions at 1000 mg or more calcium). In older persons not at high risk, benefits of vitamin D with calcium may be balanced with harms (little to no adverse events, such as GI and renal, and the uncertain risk of myocardial infarctions at 1000 mg or more calcium). In older persons at any risk, the little to no benefits of vitamin D alone or calcium alone are balanced with harms.	High risk Yes ☐ No X Not at high risk Yes ☐ No X

<table>
<tr>
<td></td>
<td>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 older men; and there was fair evidence of association with increased risk of falls and serum 25OHD levels in institutionalized older people.

IOM recommendations and Canadian RDA (>70 years):
Vitamin D: ERA 400IU, RDA 800 IU
Calcium: ERA 1000 mg, RDA 1200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values and preferences
Are you confident about the assumed or identified relative values and are they similar across the target population?
The more certainty or similarity in values and preferences, the more likely a strong recommendation</td>
<td>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.

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.

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).</td>
<td>High value on avoiding hip fractures and falls which may result in serious injury, fear of falling, and burden to staff.
Low value on small and uncertain risk of adverse events. However, all adverse events of supplements would be avoided with adequate dietary intake.</td>
<td>Yes No
X ☐</td>
</tr>
<tr>
<td>Resource implications
Are the resources worth the expected net benefit from following the recommendation?

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.</td>
<td>Annual cost per 1000 older persons at high risk of fractures
<table>
<tr><th></th><th>Vit D alone</th><th>Vit D with calcium</th><th>Calcium alone</th></tr>
<tr><td>Supplement (≥800 IU D_3, ≥500mg Ca)</td><td>$72,000</td><td>$136,000</td><td>$64,000</td></tr>
<tr><td>Hip fracture</td><td>-$216,000</td><td>-$540,000</td><td>$288,000</td></tr>
<tr><td>Vertebral fracture</td><td>-$36,000</td><td>-$12,000</td><td>-$294,000</td></tr>
<tr><td>Nonvertebral fracture</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>
</table></td>
<td>Costs of supplements not consistently funded across provinces. However, costs appeared worth the net benefit in older persons at high risk of fractures.</td>
<td>Yes No
X ☐</td>
</tr>
</table>

BASELINE COSTS

Annual cost per 1000 older persons

	Vit D alone	*Vit D with calcium*	*Calcium alone*
Supplement (≥800 IU D_3, ≥500mg Ca)	$72,000	$136,000	$64,000
Hip fracture	$72,000	-$180,000	$108,000
Vertebral fracture	-$6,000	$0	-$36,000
Nonvertebral fracture	$0	-$11,000	$0
TOTAL	$66,000	-$191,000	$72,000

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

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** **2 more per 1000** (3 fewer to 7 more) **High risk** **6 more per 1000** (10 fewer to 20 more)	**OR 0.73** (0.59 to 0.91)	**Overall risk** **5 fewer per 1000** (2 to 8 fewer) **High risk** **15 fewer per 1000** (5 to 24 fewer)	**OR 1.14** (0.82 to 1.59)	**Overall risk** **3 more per 1000** (4 fewer to 11 more) **High risk** **8 more per 1000** (10 fewer to 32 more)	**Overall risk** 20 hip fractures per 1000 **High risk** 60 hip fractures per 1000
	Based on 7225 participants, 3 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		Based on 3853 participants, 2 trials ⊕⊕⊕⊖ **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		Based on 139 647 participants, 40 trials ⊕⊕⊕⊖ **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** **1 fewer per 1000** (8 fewer to 11 more) **High risk** **6 fewer per 1000** (71 fewer to 83 more)	**OR 0.99** (0.74 to 1.41)	**Overall risk** **0 fewer per 1000** (5 fewer to 8 more) **High risk** **2 fewer per 1000** (44 fewer to 61 more)	**OR 0.71** (0.45 to 1.12)	**Overall risk** **6 fewer per 1000** (11 fewer to 2 more) **High risk** **49 fewer per 1000** (99 fewer to 19 more)	**Overall risk** 20 vertebral fractures per 1000 **High risk** 200 vertebral 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; consistent with Avenell 2009		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		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		

Outcomes	Effects and Quality of the Evidence						
	Vitamin D without calcium		Vitamin D with calcium		Calcium		Placebo/no treatment
Nonvertebral fractures	OR 1.01 (0.85 to 1.20)	Overall risk **0 more per 1000** (3 fewer to 4 more) High risk **1 more per 1000** (9 fewer to 11 more)	OR 0.94 (0.84 to 1.02)	Overall risk **1 fewer per 1000** (3 fewer to 0) High risk **3 fewer per 1000** (9 fewer to 1 more)	OR 1.00 (0.83 to 1.22)	Overall risk **0 fewer per 1000** (3 fewer to 4 more) High risk **0 fewer per 1000** (10 fewer to 12 more)	Overall risk 20 nonvertebral fractures per 1000 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)		

Outcomes	Effects and Quality of the Evidence						
	Vitamin D without calcium		**Vitamin D with calcium**		**Calcium**		**Placebo/no treatment**
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 ⊕⊕⊖⊖ **low** Risk of bias, imprecision (Cameron 2012); consistent with Murad 2011, all population 0.97(0.84-1.11)		Based on 583 participants, 1 trial ⊕⊕⊕⊖ **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.		Based on 2643 participants, 1 trial ⊕⊕⊖⊖ **low** Indirect: community only, measured 1 week after 4 months; imprecise; HR 0·89 (0·77–1·02) (Grant 2005)		
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.**		**No differences in quality of life.**		**No differences in quality of life.**		0.7 on EQ-5D
	Based on 5292 participants, 1 trial ⊕⊕⊕⊖ **moderate** Indirect: community only (Grant 2005)		Based on 5292 participants, 1 trial ⊕⊕⊕⊖ **moderate** Indirect: community only (Grant 2005)		Based on 5292 participants, 1 trial ⊕⊕⊕⊖ **moderate** Indirect: community only (Grant 2005)		
	Effects and Quality of the Evidence						

Outcomes	Vitamin D without calcium		Vitamin D with calcium		Calcium		Placebo/no treatment
Myocardial infarction	**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
	Based on 39 879 participants, 6 trials ⊕⊕⊖⊖ **low** 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		Based on 20 090 participants, 3 trials ⊕⊕⊖⊖ **low** 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		10210 participants, 6 trials ⊕⊕⊖⊖ **low** 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		
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		200 GI events per 1000
	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**	6 hypercalcaemia 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**	**17 renal diseases 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.
- **Autier** P, Gandini S, Mullie P. A systematic review: influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. J Clin Endocrinol Metab. 2012 Aug;97(8):2606-13.
- **Avenell** A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2009;2:CD000227. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009; 169:551-61.
- **Bischoff-Ferrari** HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009; 169:551-61.
- **Bischoff-Ferrari** HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, Flicker L, Wark J, Jackson RD, Cauley JA, Meyer HE, Pfeifer M, Sanders KM, Stähelin HB, Theiler R, Dawson-Hughes B. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med. 2012 Jul 5;367(1):40-9.
- **Bolland** MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. The Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010 Jul; 29 (341)c:3961.
- **Bolland** MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011 Apr 19;342:d2040.
- **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.
- **Canadian Pharmacists Association**. Compendium of Pharmaceuticals and Specialties. Canadian Pharmaceutical Association. Toronto ON.
- **Elamin** MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ, Hensrud DD, Murad MH, Montori VM. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011 Jul;96(7):1931-42.
- **Gillespie** LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012 Sep 12;9:CD007146.
- **Levis** S. Theodore G. Summary of AHRQ's comparative effectiveness review of treatments to prevent fractures in men and women with low bone density or osteoporosis: update of the 2007 report. J Manag Care Pharm 2012; 18(4 Suppl B) S1-15.

- **Muir** SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2011 Dec;59(12):2291-300.
- **Murad** MH, Elamin KB, Abu Elnour No, Elamin MB, Alkatib AA, Fatourechi MM, Almandoz JP, Mullan RJ, Lane MA, Liu H, Erwin PJ, Hensrud DD, Montori VM. Clinical Review: The effect of vitamin D on falls: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011 Oct; 96(10):2997-3006.
- **Murad** MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, Abu Elnour NO, Erwin PJ, Hazem A, Puhan MA, Li T, Montori VM. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2012 Jun;97(6):1871-80.
- **Rejnmark** L, Avenell A, Masud T, Anderson F, Meyer HE, Sanders KM, Salovaara K, Cooper C, Smith HE, Jacobs ET, Torgerson D, Jackson RD, Manson JE, Brixen K, Mosekilde L, Robbins JA, Francis RM, Abrahamsen B. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab. 2012 Aug;97(8):2670-81.
- **Ross** AC, Taylor CL, Yaktine AL, Del Valle HB, Editors; Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine. Appendix C: Methods and Results from the AHRQ-Ottawa Evidence-Based Report on Effectiveness and Safety of Vitamin D in Relation to Bone Health. In Dietary Reference Intakes for Calcium and Vitamin D, 2011. Available at http://www.nap.edu/catalog.php?record_id=13050.
- **Sawka** AM, Ismaila N, Cranney A, Thabane L, Kastner M, Gafni A, Woodhouse LJ, Crilly R, Cheung AM, Adachi JD, Josse RG, Papaioannou A. A scoping review of strategies for the prevention of hip fracture in elderly nursing home residents. PLoS One. 2010 Mar 3;5(3):e9515.

Randomised controlled trials

- **Grant** AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, Anderson FH, Cooper C, Francis RM, Donaldson C, Gillespie WJ, Robinson CM, Torgerson DJ, Wallace WA; RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet. 2005 May 7-13;365(9471):1621-8.
- **Reid** IR, Mason B, Horne A, Ames R, Reid HE, Bava U, Bolland MJ, Gamble GD. Randomized controlled trial of calcium in healthy older women. Am J Med. 2006 Sep;119(9):777-85.

A5. Pharmacological Therapies

Should pharmacological therapies to prevent fractures be recommended for older people in long-term care?

A5.1 Recommendations, Remarks, and Evidence Summary

RECOMMENDATIONS

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 adverse effects, such as atypical femoral fractures. Alendronate and risedronate are recommended as first line therapies because of their relatively low cost compared to other therapies. Tablets of alendronate and risedronate are not to be crushed, and these drugs are to be provided to older persons who can remain upright for 30 minutes after administration. Some formulations must be administered to at least 30 minutes before food intake. Other formulations can be taken with food.

For the older persons who cannot swallow or have difficulty taking oral medications, alternative first line therapies are available (see below for recommendations for denosumab and zoledronic acid). The product monographs indicate that alendronate and risedronate are not recommended for older people 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 that zoledronic acid be used as first line therapy (strong recommendation, moderate quality evidence).

Remarks: The probable reductions in fractures (hip, vertebral and nonvertebral) and mortality with zoledronic acid slightly outweigh the uncertain increased risk of musculoskeletal adverse effects (e.g. arthralgia, myalgia) and the higher costs when compared to other first line therapies. This recommendation applies to older persons who have difficulty taking oral medications because of dysphagia, an inability to sit up for 30 minutes, cognitive impairment, or intolerance. The product monograph for zoledronic acid 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 affect renal function http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/14383a-eng.php; that creatinine clearance should be monitored before and periodically after treatment; that appropriate hydration (500 mL of water) is necessary before and after treatment; and that this medication should not be given to people with severe renal impairment (creatinine clearance < 30 mL/min).

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

Remarks: The reductions in fractures (hip, vertebral and nonvertebral) and mortality with denosumab slightly outweigh the small and uncertain risk of serious infections and greater cost relative to other first line therapies. This recommendation applies to older persons who have difficulty taking oral medications because of dysphagia, an inability to sit up for 30 minutes, cognitive impairment, or intolerance. Although denosumab may be prescribed for residents with renal impairment, the product monograph for denosumab indicates that in clinical studies, patients with renal impairment (creatinine clearance < 30mL/min) and those receiving dialysis were at greater risk of hypocalcaemia than those without renal impairment.

For residents who are at HIGH RISK OF FRACTURES, we <u>suggest</u> 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 access to this medication, and there may be a higher burden because of the need for daily injections. A low value was placed on the uncertain effect of teriparatide on back pain because of past and future vertebral fractures, and on hip fractures.

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

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

For residents who are at HIGH RISK of FRACTURES, we <u>suggest</u> that 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) with etidronate. The cost of this drug is, given the lack of important benefits.

<u>Evidence summary:</u> There is moderate quality evidence for pharmacological therapies from network meta-analyses of randomised controlled trials involving more than 100 000 people at high risk of fractures (Hopkins 2011; AHRQ 2012; Murad 2012). There was risk of bias in some studies and uncertainty when the effects in post-menopausal women were applied to long-term care residents. Results showed probable reductions in hip fractures of approximately **25 per 1000 fewer** across all drugs, but relatively smaller reductions with etidronate and raloxifene. Evidence also showed probable reductions in vertebral fractures (approximately **100 fewer per 1000)** and non-vertebral fractures (approximately **20 per 1000 fewer**) with all drugs, but relatively greater reductions with teriparatide, and smaller reductions with raloxifene. Systematic reviews showed reductions in mortality rates may be likely with bisphosphonates (10 per 1000 fewer: 95% CI, 22 fewer to 3 more),

raloxifene (10 per 1000 fewer: 95% CI, 21 to 0 fewer); or denosumab (**23 per 1000 fewer: 95% CI, 46 fewer to 6 more**) (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 or delayed healing (estimated at <1/10 000 in community dwelling older people) (Rizzoli 2011; Rizzoli 2007; Rizzoli 2011). It is unclear whether these risks would be higher in long-term care residents. The evidence for the risk of atrial fibrillation with bisphosphonates (Mak 2009), and cerebrovascular/cardiovascular events with raloxifene (Grady 2010) was also of low quality; these results were imprecise and include the possibility of small to no increases in these events. Venous thromboembolism may increase with raloxifene (12 per 1000 more: 95% CI, 7 to 19 more))(Grady 2010); musculoskeletal events may increase with zoledronic acid (146 per 1000 more: 95% CI, 125 to 169 more) (Hadji 2012); and serious infections may increase with denosumab (8 per 1000 more: 95% CI, 0 to 18 more) (Toulis 2010)). Randomised controlled trials and pharmacovigilance for bisphosphonates and raloxifene showed little to no effect of these drugs on serious gastrointestinal events (AHRQ 2012).

We estimated that direct drug costs were worth the overall beneficial consequences of most drugs with the exception of etidronate and raloxifene. The costs of teriparatide, denosumab and zoledronic acid were also high relative to those of other therapies.

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

QUESTION

Population	Older people 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
Quality of evidence (QoE) *Is there high or moderate quality evidence?* The higher the quality of evidence, the more likely is a strong recommendation	**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.		Yes ☐ No X
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burden or vice versa?* 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.	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 Probably reductions in mortality across all drugs with **~10 fewer** with bisphosphonates and raloxifene; may be greater reduction with denosumab (**23 fewer**) May have little to no effect on quality of life, but probable reduction in back pain reported for teriparatide 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.	For most therapies, benefits clearly outweigh harms. Risks of harms may occur or are uncertain due to few long term studies or post-marketing. However, there were very small and/or uncertain benefits with etidronate and raloxifene.	Yes X No ☐ Yes ☐ No X

	Burden of therapies to staff and/or older persons: 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.		
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	Review reported preference for less frequent dosing preferred (weekly over daily; annually over weekly, IV over oral), but adverse events more important than frequency (also regardless of efficacy). Downstream consequences of hip fractures: 50-80% greater mortality; 65% lose mobility; meaningful loss in quality of life.	High value was placed on avoiding serious consequences of fractures. Low value was placed on minor adverse events (e.g. gastrointestinal) or uncertain adverse events (e.g. serious infections).	Yes X No ☐
Resource implications *Are the resources worth the expected net benefit from following the recommendation?* 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.	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. See Table page 28.	Costs of teriparatide, denosumab and zoledronate were high relative to the other therapies leading to recommendations for those therapies in high risk older people who could not take oral medications.	Yes X No ☐

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 older 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 older people 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 ≥ 800 IU and Calcium ≥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 older persons 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

A5.3 Evidence Profile

Drug therapies to prevent fractures in older persons 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) **24 fewer per 1000** (14 to 32 fewer)	**OR 0.48** (0.31 to 0.66) **23 fewer per 1000** (15 to 31 fewer)	**OR 0.50** (0.34 to 0.73) **22 fewer per 1000** (12 to 29 fewer)	**OR 1.02** (0.12, 3.91) **1 more per 1000** (39 fewer to 111 more)	**OR 0.42** (0.10 to 1.82) **26 fewer per 1000** (40 fewer to 34 more)	**OR 0.87** (0.63 to 1.22) **6 fewer per 1000** (16 fewer to 9 more)	**OR 0.50** (0.27 to 0.86) **22 fewer per 1000** (6 to 32 fewer)	45 hip fractures per 1000 (no calcium or Vitamin D - 60 hip fractures per 1000)
Vertebral fractures	**OR 0.50** (0.33 to 0.79) **89 fewer per 1000** (35 to 124 fewer)	**OR 0.46** (0.31 to 0.68) **97 fewer per 1000** (55 to 128 fewer)	**OR 0.35** (0.20 to 0.64) **120 fewer per 1000** (62 to 152 fewer)	**OR 0.61** (0.29 to 1.08) **68 fewer per 1000** (132 fewer to 13 more)	**OR 0.30** (0.16 to 0.55) **130 fewer per 1000** (79 to 162 fewer)	**OR 0.57** (0.39 to 0.83) **75 fewer per 1000** (28 to 111 fewer)	**OR 0.33** (0.19 to 0.65) **124 fewer per 1000** (60 to 155 fewer)	**200 vertebral fractures per 1000**
Non vertebral fractures	**OR 0.78** (0.66 to 0.92) **13 fewer per 1000** (5 to 20 fewer)	**OR 0.68** (0.55 to 0.81) **18 fewer per 1000** (11 to 26 fewer)	**OR 0.69** (0.55 to 0.84) **18 fewer per 1000** (9 to 26 fewer)	**OR 0.64** (0.31 to 1.27) **21 fewer per 1000** (41 fewer to 15 more)	**OR 0.50** (0.32 to 0.78) **29 fewer per 1000** (13 to 40 fewer)	**OR 0.90** (0.76 to 1.03) **6 fewer per 1000** (14 fewer to 2 more)	**OR 0.74** (0.56 to 0.94) **15 fewer per 1000** (3 to 25 fewer)	**60 nonvertebral fractures per 1000**

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 - 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)			Based on 59,209 participants, 30 trials. ⊕⊕⊕⊖ **moderate** From network meta-analysis with trials with risk of bias; population primarily community (Hopkins 2011)	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)			
Mortality	**Bisphosphonates only RR 0.91** (0.80 to 1.03) **10 fewer per 1000** (22 fewer to 3 more)			Not reported	Not reported	**HR 0.90** (0.80 to 1.00) **10 fewer per 1000** (21 fewer to 0)	**RR 0.78** (0.57 to 1.06) **23 fewer per 1000** (46 fewer to 6 more)	**110 deaths per 1000** (No calcium and Vitamin D - 120 deaths per 1000)
	Based on 32 880 participants, 8 trials. ⊕⊕⊕⊖ **moderate** Indirect - community population; some risk of bias (Bolland 2010)					**Based on 15324 participants, 2 trials** ⊕⊕⊕⊖ **moderate** Some risk of bias; Indirect - community population at risk coronary disease (Grady 2010)	Based on 7808 participants, 1 trial ⊕⊕⊖⊖ **low** Imprecision; indirect - community population; some risk of bias (Bolland 2010)	
Quality of life (including	No significant difference with	Not reported	No meaningful differences with	Not reported	**RR 0.60** (0.48 to 0.75)	No significant difference	No significant difference	**Back pain 130/1000 per**

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**				
pain)	zoledronate		placebo at 1,2,3 years		52 fewer per 1000 (62 to 33 fewer)			**1000**
	Based on 599 participants, 1 trial ⊕⊕⊕⊖ **low** Imprecision; Risk of bias; indirect population (Hadji 2012)		Based on 1434/7765 participants, 1 trial ⊕⊕⊕⊖ **low** Imprecision; Risk of bias; indirect population (Sambrook 2011)		Based on 2 670 participants,5 trials ⊕⊕⊕⊖ **low** Some risk of bias; Indirect – comm-unity population, imprecision (Nevitt 2006)	Based on 129 participants, 1 trial ⊕⊕⊕⊖ **low** Risk of bias; imprecision; indirect population (Jacobsen 2012)	Based on 7808 participants, 1 trial ⊕⊕⊕⊖ **moderate** Some risk of bias; Indirect - community population (Silverman 2012)	
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 frax healing	6/10 000 (Rizzoli 2011)			Not reported	Not reported	Not reported	Not reported	**3/10 000** (no 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** *

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**				
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 gastro-intestinal 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** *
Musculo-skeletal (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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- **MacLean** C, Alexander A, Carter J, et al. Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2007 Dec. (Comparative Effectiveness Reviews, No. 12.) 3, Results. Available from: http://www.ncbi.nlm.nih.gov/books/NBK43169/
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- **Nevitt** MC, Chen P, Dore RK, Reginster JY, Kiel DP, Zanchetta JR, Glass EV, Krege JH. Reduced risk of back pain following teriparatide treatment: a meta-analysis. Osteoporos Int. 2006 Feb;17(2):273-80.
- **Rizzoli** R, Reginster JY, Boonen S, Bréart G, Diez-Perez A, Felsenberg D, Kaufman JM, Kanis JA, Cooper C. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. Calcif Tissue Int. 2011 Aug;89(2):91-104.
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International Osteoporosis Foundation Working Group Report. Osteoporos Int. 2011 Feb;22(2):373-90.

- **Wells** GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003376.
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Randomised controlled trials

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A6. Hip Protectors

Should hip protectors be recommended for older persons in long-term care to prevent fractures?

A6.1 Recommendations, Remarks, and Evidence Summary

RECOMMENDATIONS

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

Remarks: These recommendations place a high value on avoiding the serious consequences of hip fractures in mobile residents, including pain, loss of mobility and death. A lower value was placed on the cost or burden for an individual or for the long-term care home's resources. Given the small reductions in hip fractures achieved with hip protectors, older persons who are not at high risk may choose alternative options to prevent hip fractures. It is recognised that adherence to a recommendation to wear hip protectors may be challenging, and therefore strategies to improve adherence may be needed. This recommendation applies to hard or soft hip protectors and the choice between them 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%) among older persons wearing hip protectors in institutional settings (Santesso 2014). Over one year, 4 fewer hip fractures (95% CI, 0 to 7 fewer) per 1000 older persons wearing hip protectors may be likely, and among older persons at higher risk, 11 fewer per 1000 (95% CI, from 0 to 20 fewer) may be likely. However, 1 more pelvic fracture (95% CI, 0 to 4 more) per 1000 older persons not at high risk, and 8 more (95% CI, from 3 fewer to 30 more) per 1000 older persons at high risk may be likely. Moderate evidence also showed that there is probably little or no difference in the frequency of 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 were 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 observed may represent the true effects when this strategy is implemented.

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

QUESTION

Population	Older people 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) *Is there high or moderate quality evidence?* 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 ☐
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burden or vice versa?* 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 older persons at risk of hip fractures, there is a small net benefit of hip protectors. In older persons at high risk of hip fractures, there is a large net benefit of hip protectors.	Overall risk Yes No ☐ X High risk Yes No X ☐
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?* 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 ☐ X

Resource implications

Are the resources worth the expected net benefit from following the recommendation?

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.

Difference in annual cost per 1000 with hip protector

	Overall risk	***High risk***
*Three soft hip protectors **($240)***	*+$240 000*	*+$240 000*
Hip fracture	*-$144 000*	*-$396 000*
*Pelvic fracture**	*+$11 000*	*+$88 000*
TOTAL	***+$107 000***	***-$68 000***

*Three soft hip protectors **($120)***	*+$120 000*	*+$120 000*
Hip fracture	*-$144 000*	*-$396 000*
*Pelvic fracture**	*+$11 000*	*+$88 000*
TOTAL	***-$12 000***	***-$188 000***

Note: cost for staff resources in institutions not considered

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].

The benefits of the hip protectors do not outweigh the costs in older persons at risk of hip fractures. However, the benefits do outweigh the costs in older persons at high risk.

Overall risk

Yes	No
☐	X

High risk

Yes	No
X	☐

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 in older persons in long-term care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects per year Risk with No hip protectors	 Risk difference with Hip protectors (95% CI)
Number of people 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 people 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 person 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**[1,5] 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 in older people 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 2014 Mar 1;3:CD001255.
- **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. Osteoporos Int, 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 older persons in long-term care to prevent fractures?

A7.1 Recommendations, Remarks and Evidence Summary

RECOMMENDATIONS

For residents who are 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 that is achieved with exercise, as falls may lead to serious injuries. It also places a high value on the other benefits that exercise could provide and a lower value on the uncertain costs to implement exercise interventions in long-term care settings.

For residents who are at HIGH RISK of FRACTURES, we suggest balance, strength and functional training exercises only when such exercises are 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 that may occur among individuals at high risk of falls who participate in exercises, such as balance, strength and functional training. Some older persons may value exercising despite the potential risk of falls. When exercise is made available to residents, it should be provided as part of a multifactorial intervention to prevent falls (including medication review (eg., using the Beers Criteria http://geriatricscareonline.org/ProductAbstract/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001)), assessment of environmental hazards, or use of assistive devices), or with other interventions to prevent fractures (including vitamin D and calcium supplementation, hip protectors, and pharmacological therapies).

Evidence Summary: These recommendations are based on systematically reviewed evidence that is of moderate to low quality (Cameron 2012). This review included subgroup analyses for older persons in high level care and intermediate care facilities, which were 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.

Subgroup analyses for high-level v. intermediate-level care among older residents at high risk of fractures suggest increases in the number of falls (870 more per 1000 older people: 95% CI, from 210 fewer to 2370 more), or the number of older persons falling (85/1000 more: 95% CI, from 20 fewer to 210 more). Among older persons *not* at high risk of fractures, the analyses suggest reductions in the number of falls (660 fewer per 1000 older people: 95% CI, from 1290 fewer to 390 more), or the number of older people falling (20 per 1000 fewer: 95% CI, from 115

fewer to 105 more). These results were from studies that evaluated balance training (such as Tai Chi), strength training and functional training. One study measured hip fractures, but the results were uncertain because there were very few events. A systematic review of exercise as part of a multifactorial intervention to prevent falls showed that the multifactorial intervention may reduce falls (660 fewer falls per 1000 people per year: 95% CI, from 1230 fewer to 120 more), reduce the number of older people who fall (55 fewer per 1000: 95% CI, from 115 fewer to 10 more) and hip fractures (10 fewer per 1000: 95% CI, from 14 fewer to 1 more) (Cameron 2012).

A7.2 Question, Evidence to Recommendations Table for Exercise

QUESTION

Population	Older people 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
Quality of evidence (QoE) *Is there high or moderate quality evidence?* The higher the quality of evidence, the more likely is a strong recommendation	**QoE for benefits:** Moderate to low **Key reasons for downgrading the evidence:** Risk of bias and unexplained heterogeneity (data for older people in high care facilities applied to older people at high risk of fractures). There was no data for outcomes such as quality of life, mobility, pain, etc.		Yes No ☐ X
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burden or vice versa?* 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.	For older people at high risk of fractures, exercise: -may increase number of falls, 870 more falls per 1000 people (-210 to +2370) -may increase number of older persons falling, 85/1000 more (-20 to +210) For older people not at high risk of fractures, exercise: -probably reduces number of falls, 660 fewer falls per 1000 people (-1290 to +390) - probably small reduction in number of older persons falling, 20/1000 fewer (-115 to +105) 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. Exercise as part of a multifactorial intervention may reduce falls (660 fewer falls per 1000 older persons per year, -1230 to 120), reduce the number of older persons who fall (55/1000 fewer will fall per year, -115 to 10) and reduce hip fractures (10 fewer per 1000 people per year, -14 to 1).	The harms may outweigh the benefits in older people at high risk of fractures. However, when exercise is part of a multifactorial intervention benefits slightly outweigh harms. The benefits slightly outweigh harms in older people not at high risk of fractures.	High risk Yes No ☐ X Not at high risk Yes No X ☐
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	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). 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.	High value placed on avoiding a fall which may lead to serious injuries, resident fear of falling, and burden to facility staff.	Yes No X ☐

	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.		
Resource implications *Are the resources worth the expected net benefit from following the recommendation?* 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.	Access to physiotherapy, physiotherapists and assistants, kinesiologists is currently available in long-term care with some variability across provinces. There is little research about the costs and resources required to provide specific exercise interventions in long term care.	Resources likely worth the benefits in older people at low risk	Yes X No ☐

A7.3 Evidence Profile regarding Exercise

Exercise compared to Usual Care in older persons 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 people per year	625 (4 studies)	⊕⊕⊖⊖ **LOW**[1,2,3] due to risk of bias, imprecision	**Rate Ratio 1.29** (0.93 to 1.79)	**3000 falls per 1000 people**	**870 more falls per 1000 people** (from 210 fewer to 2370 more)
Number of people 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 people fall per 1000**	**85 more people fall per 1000** (from 20 fewer to 210 more)
Number of people 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 older persons NOT AT HIGH risk of fractures in long-term care

Number of falls per 1000 people per year	1229 (4 studies)	⊕⊕⊕⊖ **MODERATE**[1,2] due to risk of bias	**Rate Ratio 0.80** (0.57 to 1.13)	**3000 falls per 1000 people**	**660 fewer falls per 1000 people** (from 1290 fewer to 390 more)
Number of people 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 people fall per 1000**	**20 fewer people fall per 1000** (from 115 fewer to 105 more)
Number of people 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

- **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.

A8. Multifactorial Interventions

Should multifactorial interventions to prevent fractures be recommended for older persons 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 to reduce falls that are tailored to an individual's risk. These interventions may include medication reviews (eg., using the Beers Criteria http://geriatricscareonline.org/ProductAbstract/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001), assessment of environmental hazards, use of assistive devices, exercise, management of urinary incontinence, and educational interventions directed to staff. This recommendation is conditional because of 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 should 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 because of 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, the systematic review suggests reductions in the number of falls (660 fewer falls per 1000 older persons per year [1230 fewer to 120 more]), and the number of residents who fell (55 fewer older persons per 1000 (95% CI, 115 fewer to 10 more) with the application of multifactorial interventions. There was low quality of evidence for a reduced risk of hip fractures (10 fewer per 1000: 95% CI, 14 fewer to 1 more). 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	Older people 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
Quality of evidence (QoE) *Is there high or moderate quality evidence?* The higher the quality of evidence, the more likely is a strong recommendation	**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.		Yes ☐ No X
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burden or vice versa?* 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.	With multifactorial interventions, there - May be 660 fewer falls per 1000 (--1230 to 120) people per year - May be 55 fewer (-115 to 10) people will fall per year - May be 10 fewer hip fractures (-14 to 1) per 1000 people per year Harms were not reported and information from observation would suggest no potential for other harms. There was no significant interaction between studies with older persons in high or mixed levels versus intermediate levels of care, or in older persons with higher or lower cognition. The effects of different combinations of interventions is uncertain due to insufficient data. The effects of exercise interventions alone in older persons at high risk of fractures may increase falls and the number of fallers.	The benefits slightly outweigh any harms that may occur.	Yes X No ☐
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	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). 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.	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.	Yes X No ☐

	The panel felt that a high value should be placed on increased fear of falling in older persons and likely the additional burden to staff when residents fall.		
Resource implications *Are the resources worth the expected net benefit from following the recommendation?* 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.	The costs of implementation of multifactorial interventions was not determined and there is little to no research about costs. There may be high human and financial costs to implement multifactorial interventions across all residents in long-term care. The costs of different interventions will also vary.	The costs of the interventions may outweigh the serious consequences and costs of fractures; but will vary across settings A low value has been placed on costs of interventions in long-term care	Yes ☐ No X

A8.3 Evidence Profile regarding Multifactorial Interventions

Multifactorial interventions compared to Usual Care for older persons 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 people 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 people	**660 fewer falls per 1000 people** (from 1230 fewer to 120 more)
Number of people 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 people fall per 1000	**55 fewer people 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 people	**10 fewer per 1000 people** (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.