APPENDIX 2: Supplementary Material

2023 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF OSTEOPOROSIS AND FRACTURE PREVENTION IN CANADA

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CONFLICT OF INTEREST

Appendix 2, as supplied by the authors. Appendix to: Morin SN, Feldman S, Funnell L, et al. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. *CMAJ* 2023. doi: 10.1503/cmaj.221647.

EVIDENCE TO DECISION TABLES (50)

Appendix 2, as supplied by the authors. Appendix to: Morin SN, Feldman S, Funnell L, et al. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. *CMAJ* 2023. doi: 10.1503/cmaj.221647.

CONFLICT OF INTEREST

A) Conflict of Interest Guidelines for Osteoporosis Canada Guideline Steering Committee and Working Groups.

Fall 2017

The Conflict of Interest Oversight Committee provides review and commentary regarding levels of real/potential conflict of interest as declared by members of the Scientific Advisory Council (SAC) and others who may be asked to participate in the Guideline working groups. This committee is advisory to the Chair of the SAC of Osteoporosis Canada (OC) and Chair of the Guidelines Working Groups.

Background:

- Conflict of Interest is "a set of conditions in which professional judgement concerning a primary interest (e.g., patient's health care) is unduly influenced by a secondary interest" (1) (e.g., author's financial or intellectual interests)
- Intellectual COIs are "academic activities that create the potential for an attachment to a specific point of view that could unduly influence the individual's judgment about a specific recommendation" (2)
- The Conflict of Interest Oversight committee will work to ensure that Conflicts of Interest are disclosed and prospectively managed in a transparent manner to ensure that the 2019 Guidelines can be viewed as trusted resource regarding osteoporosis care in Canada

Implementation COI Guidelines for the 2023 Guideline Update Groups
Goal: to identify and mitigate/minimize, as much as possible, conflicts which could consciously or unconsciously bias the efforts of the 2023 Guideline Update Group and eventual writing of the new Guideline.

Timelines regarding COI restrictions

- Nov 2016 to Nov 2020
    - 1 year prior to the beginning of the development process (Nov 2017)
    - duration of the development and writing process
    - 1 year after publication of the Guidelines document (2019)

Recommendations for all Working Groups to mitigate Conflicts of Interest

- All participants for potential inclusion in the Guideline process must submit a COI document for review and adjudication by the COI Oversight Committee (COI-OC)

- COI disclosures must be filed annually in writing for review

- COI must be declared verbally by the individual at the beginning of each working meeting for the Chair to determine if a stated conflict may impact the meeting deliberations. If concerns of potential impact are determined, the Chair may

exclude the member from components of the discussion, deliberations or the vote.

- COI documents are adjudicated as:
    - No Relevant Conflict is defined as no financial relationship(s) related to osteoporosis research/care or otherwise between any commercial partner and the individual, on their behalf to an institution or involving family members
        - *Eligible for full participation in any component of the Guidelines Development process*

    - Manageable conflict is defined as a financial relationship that <u>is not directly</u> relevant to osteoporosis research/care between a commercial partner and the individual, on their behalf to an institution or involving family members
        - *Eligible to participate in the elements of the guideline development process but may be asked to abstain from voting by the Working Group Chair if, at the discretion of the guidelines working group and the COI Committee, the conflict could potentially influence or be perceived to influence the decisions of the committee*
        - *Financial gain of $5000.00 Cdn or less from any/all commercial sources is deemed "manageable".*

    - Significant Conflict - (perceived or real) is defined as a financial relationship that <u>is directly</u> relevant to osteoporosis research/care between a commercial partner and the individual, on their behalf to an institution or involving family members
        - *Eligible to provide expert opinion but must recuse themselves from voting*
        - *Financial gain of more than $5000.00 Cdn from any/all commercial sources is deemed an impactful conflict.*

- All Working Group Chairs must be free of relevant COI
- 50% of individuals on the working groups must be free of relevant COI

Examples of Conflict

- Commercial Interests - Pharmaceutical Industry Relationships
    - Monies received directly by the clinician for work done on behalf of the "company"
        - Speaker's bureau, Advisory Board, Consultancy, Industry supported research
    - Monies received by the individual to support research or educational activities directly under the control of the individual
        - Research grants, personal education grants,
    - Monies received by an institution to support research or educational activities directly under the control of the individual
    - Monies received from patents, copyrights licenses related to osteoporosis management/care
- Non-commercial Interests

Selected Ref:

1. NEJM 329:573-576
2. AIM 152: 738-741
3. AIM Oct 6, 2015
4. Am J Respir Crit Care Med 180: 5640-580 (2009)
5. JAMA 317: (May 2017)
6. JAMA 318: (Sept 2017)
7. ACR per Website: ACR Policy and Procedure Manual for Clinical Practice Guidelines (2015)

2019 Update

After discussion with the Steering committee and the Conflict of Interest Oversight Committee, driven by discussions within the COI-OC, the category of "manageable" conflicts of interest was eliminated and all industry based remuneration will be categorized as a Conflict of Interest.

All prior COI declarations will be reviewed and re-categorized if needed, to reflect this new and more stringent categorization.

Jurisdiction for the COI process will be removed from OC for the Guideline Steering Committee and all members of the Guideline Working Groups and will be fully managed and adjudicated by the COI-OC.

B) 2023 Conflict of Interest Oversight Committee Summary of Process

The process for minimizing risk of conflict of interest (COI) was developed for the explicit purpose of managing competing or conflicting interests during the development and writing of the Clinical Practice Guideline. In September 2017, a Conflict of Interest Oversight Committee was created and comprised of a Chair (HMB), the Vice Chair of the Scientific Advisory Committee (RR), a family physician and patient representatives.
Revisions were made in 2019 as the guideline development began which made the process arm's length from OC leadership.

The COI Oversight Committee completed a review of key articles in the literature. Included and pivotal to the framework were the recommendations from the Guidelines International Network Principles for Disclosure and the International Committee of Medical Journal Editors (http://www.icmje.org). The COI Oversight Committee developed recommendations defining, identifying and managing potential conflicts. The recommendations were reviewed by the executive committee of the Scientific Advisory Council and then disseminated to Guideline Steering Committee, Working Group chairs and members of the guidelines writing groups.

The COI Oversight Committee undertook the process of annual monitoring of declarations of COI from all members of the guideline working groups. The data collection form was updated to reflect the International Committee of Medical Journal Editors proposed disclosure process. Each August, the COI declarations were collected and reviewed and for those members of the

Working Groups, the data tabulated and supplied to the WG chairs.

C) Adherence to the Guideline International Network Principles for Disclosure

Principle 1: Guideline developers should make all possible efforts to not include members with direct financial or relevant indirect conflicts of interests (COIs).
At the beginning of the planning process to update the Guideline, it was recognized that some Canadian experts in the diagnosis, management, and care of patients with osteoporosis could have conflicts of interest. To benefit from their perspectives and expertise but to minimize the potential impact of COI -related biases, it was predetermined that all Working Group chairs and a minimum of 50% of each Working Group membership would be free of financial competing interests for an interval spanning at least one year before to one year following the formal guidelines development process. Additionally, Chairs were identified who did not have significant non-financial conflicts. Members of a Working Group with a financial conflict were not allowed to vote on recommendations.

Conflicts of interest were adjudicated via annual submission to the Conflict of Interest Oversight Committee (HMB, RR and depending on the year, a family physician and/or community representatives) and by verbal updates to respective Chairs at each Working Group meeting. Institutional COI was managed through an arm's length relationship with Osteoporosis Canada leadership who did not sit on the Steering Committee or any of the Working Groups. Four members (SK, HF, CT and RR) of working groups sat as members of Osteoorosis Canada Board of Directors between 2019 and 2022. A review of the minutes of each of those meetings revealed that there was either no discussion about the guideline work or the board was informed about the progress but not the content of the work.

Principle 2: The definition of COI and its management applies to all members of a guideline development group, regardless of the discipline or stakeholders they represent, and this should be determined before a panel is constituted.
Annually, all members of each Working Group and the Steering Committee submitted their COI declaration. This was reviewed by the Chair of the COI Oversight Committee. If there were areas of uncertainty, there was discussion with the rest of the COI membership. This allowed all pre-established COI guidelines to be applied to all guideline group members.

Principle 3: A guideline development group should use standardized forms for disclosure of interests.
A standardized form was used annually for collecting disclosures. The data required was based on the disclosure process of the International Committee of Medical Journal Editors (http://www.icmje.org). (Appendix 2 pages 12 - 15)

Principle 4: A guideline development group should disclose interests publicly, including all direct financial and indirect COIs, and these should be easily accessible for users of the guideline.

Public declaration of all conflicts of interest, including those of Osteoporosis Canada (as an organization) will be posted on the Osteoporosis Canada public website by the time of the Guideline publication and have been included in the submitted manuscript. (Appendix 2 pages 16 – 17)

Principle 5: All members of a guideline development group should declare and update any changes in interests at each meeting of the group and at regular intervals (for example, annually for standing guideline development groups).
Through our Guideline Steering Committee, which included all Working Group Chairs and the Chair of the COI-OC, Chairs were reminded that, as part of their routine meetings, Working Group members should report a change in their COI status if relevant. Furthermore, COI declarations were obtained yearly from all participants.

Principle 6: Chairs of guideline development groups should have no direct financial or relevant indirect COIs. When direct or indirect COIs of a chair are unavoidable, a co-chair with no COIs who leads the guideline panel should be appointed.
As part of our COI framework, Working Group chairs (or co-chair) were not allowed to have a financial or indirect relevant conflict throughout the process.

For the Exercise Working Group chair, after their component of the Guideline had been completed (reviewed and voted upon), the Chair was an invited speaker at an Ontario university and received an honorarium in March 2022 which was paid through a pharmaceutical company. The topic being presented (i.e., Exercise and Osteoporosis) was unrelated to the pharmaceutical company's product, there was no discussion of medications or the company in the presentation, and the Chair was not part of working group activities related to recommendations on risk assessment or medications. As the Exercise Working Group had completed and voted upon all its recommendations by that time and given the protracted timeline for the Guideline development process, this competing interest was adjudicated to not have impact on the manuscript content or preparation.
This COI has been noted in our manuscript declarations.

Principle 7: Experts with relevant COIs and specific knowledge or expertise may be permitted to participate in discussion of individual topics, but there should be an appropriate balance of opinion among those sought to provide input.
Experts with relevant COIs were permitted to participate in the discussion within various Working Groups, allowing their experience and expertise to be shared with the group for a given topic. Within each group, the proportion of members with COI was set to be at less than 50%. Working group members were knowledgeable regarding which of their members had financial COIs.

Principle 8: No member of the guideline development group deciding about the direction or strength of a recommendation should have a direct financial COI.
Experts with potential or stated COI were not allowed to vote on the direction or the strength of the various recommendations, either within their group or for recommendations of other

groups. The voting status of each member is noted on pages 16-17.

While all members of the working groups participated in meetings and discussions, only members with no financial competing interests were eligible to vote on the recommendations brought forward for inclusion in the Guideline. Within the working groups, specific methods for implementation varied. In two of the working groups (Nutrition and Exercise), decisions were made by consensus. The Pharmacotherapeutics working group had two members with COI. Those members did not participate in key discussions or voting regarding the recommendations. In the Fracture Risk Assessment group, members with COI participated in discussions but did not participate in voting on the recommendations or the supporting strength of evidence. This was monitored and confirmed by each Chair of the Working Groups. The final recommendations of the manuscript were arrived at by consensus of the Steering Committee and approved by voting members of the Working Groups.

Principle 9: An oversight committee should be responsible for developing and implementing rules related to COIs.

The COI Oversight Committee was struck in 2017 in preparation for the guideline work and was responsible for the process and procedures related to COI management. The initial process was updated in 2019, based on feedback from members of the COI Oversight Committee and updates needed with the initiation of the guideline writing process. Annual presentations ensured knowledge of the process and written summary documents were circulated and discussed at intervals throughout the guideline work. The Chair of the COI Oversight Committee was as an ex- officio member of the Steering Committee allowing Working Group chairs to have communication with the chair of the COI Oversight Committee as needed.

D) OC Annual Conflict of Interest Declaration Template

This document was completed annually by members of the Guideline Update Group and reviewed by the Conflict of Interest Oversight Committee. A summary was provided to Working Group Chairs to ensure their awareness of potential COI status of the members of their group.

Disclosure of Potential Conflicts of Interest
Adapted from International Committee of Medical Journal Editors (ICMJE)

Section 1: Name:

Institution/Affiliation

Section 2: Disclosures

Please complete the following re potential conflicts or dualities of interest.

From September 1, relevant year, (eg: 2019) and through the end of the relevant year + 1 (eg: 2020) calendar year, have you received or do you anticipate receiving [or your institution on your behalf] payment/services from a third party [eg. government, commercial, private foundation etc.] to support any aspect of the work being done within the Guideline development process?

(Please circle and elaborate below):
Yes ☐ No ☐
Describe:

Section 3: Relevant Financial Activities

Potential conflicts of interest are defined as per the International Committee of Medical Journal Editors [ICMJE]. Please review the **Appendix** at the end of this document.

From September 1, relevant year (e. g. 2019) and during the relevant year + 1 (e. g. 2020) **calendar year**, have you or do you anticipate having any financial relationships [irrespective of amount of compensation] that could be perceived to influence or give the appearance of potentially influencing your work within Guideline development process?

(Please circle and elaborate below)
Yes ☐ No ☐
Describe:

Below, itemize commercial relationships from all pharmaceutical, diagnostic or other commercial entities.

Members who have completed COI Declarations in the past

Please include data from September 1, relevant year to December 31, relevant year + 1

Include those activities such as but not limited to:

Speakers Bureaus, Advisory Board or other similar consultative activity,
Grants for research or educational activities,
Participation in data monitoring boards,
Funding or support for manuscripts in preparation.

Dates	Name of funding entity	Grant to Institution Y/N	Personal financial support Y/N	Non-Financial support Y/N	Brief description

If additional space required, please submit on separate sheet

<u>Section 4:</u> Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to osteoporosis?
Yes ☐ No ☐

If yes, describe:

<u>Section 5:</u> Other Relationship

From September 1, relevant year and during the relevant year + 1 calendar year, have you engaged or do you anticipating engaging in other relationships or activities that individuals or organizations could perceive to have influenced, or that give the appearance of potentially influencing your Guideline work?
Yes ☐ No ☐

If yes, describe the relationships/conditions/circumstances:

Please indicate if a first-degree relative(s) (for example - parents, spouse/de facto, children) has employment in the pharmaceutical, diagnostic or other commercial industries relevant to osteoporosis.
Yes ☐ No ☐

If yes, describe the relationships/conditions/circumstances:

Section 6: Declaration

I, _____declare that to the best of my knowledge, the only direct or indirect potential conflicts of interest which can affect the objective participation and implementation of my responsibilities are those listed above.

I declare that if additional potential conflicts of interest arise during the ensuing year, these will be made known in writing.

Date:

Signature:

Appendix:

Descriptors and Definitions

Link to: ICMJE Disclosure of Potential Conflict of Interest

Relevant financial activities

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Reference: http://www.icmje.org

E) Conflict of Interest Personal Declaration Summary

The table below summarizes the declared potential conflicts – financial and institutional based on the annual submissions of Working Group members. All declared financial conflicts are noted as "Yes" in this summary, even if they occurred in one of the years under review. (2019-2022)

Name	Working Group	Financial COI	Speaker/Ad board Honoraria	OC SAC Member	Other Institutional Interests	Voting
Ashe, Maureen	Ex	No		Yes		Yes
Bardai, Zahra	Ex	No		Yes		Yes
Bartley, Joan	Ex	No				Yes
Butt, Debra	Ex	No		Yes		Yes
Cadarette, Suzanne	Pharma	No		Yes		Yes
Chilibeck, Phil	Ex	No		Yes		Yes
Dunn, Sheila	Pharma	No				Yes
Falk, Jamie	Pharma	No				Yes
Feldman, Sidney	FRA	No		Yes		Yes
Funnell, Larry		No				Yes
Gittings, William	Nut	No				Yes
Hayes, Kaleen	Pharma	No				Yes
Holmes, Carol	FRA	No				Yes
Ioannidis, George	FRA	No		Yes		Yes
Jaglal, Susan	Pharma	No		Yes		Yes
Kim, Sandra	Pharma	No		Yes	OC Board of Directors, 2019-2020	Yes
McIntyre, Virginia	FRA	No				Yes
Morin, Suzanne	FRA	No		Yes		Yes
Nash, Lynn	FRA/Nut	No		Yes		Yes
Negm, Ahmed	FRA	No		Yes		Yes
Ponzano, Matteo	Ex	No				Yes
Ridout, Rowena	Pharma	No		Yes	OC Board of Directors, 2020-Present	Yes
Rodrigues, Isabel	Ex	No				Yes
Santesso, Nancy	Pharma	No				No
Thabane, Lehana	Ex	No				Yes
Thomas, Christine	Pharma	No			OC Board of Directors, 2019-2020	Yes
Tile, Lianne	FRA	No		Yes		Yes
Ward, Wendy	Nut	No		Yes		Yes
Binkley, Neil	FRA	Yes	Amgen (consultant)			No

Burrell, Steven	FRA	No		Yes		Yes
Cheung, Angela	FRA	Yes	Amgen, Paladin Labs	Yes	ISCD Canadian Panel Chair, Endocrine Society Clinical Guidelines Committee Member,	No
Frame, Heather	Pharma			Yes	OC Board of Directors 2019 - 2020 (Past Chair)	Yes
Giangregorio, Lora	Ex	Yes	Amgen (2022, post completion of working group's guideline recommendation, unrelated to guidelines			Yes
Josse, Robert	FRA	Yes	Amgen, Alexion, Paladin, Ultragenix	Yes		No
Khan, Aliya	FRA	Yes	Amgen, Alexion, Amolyt Ascendis,Takeda	Yes		No
McDonald-Blumer Heather		Yes	Eli Lilly, Novartis	Yes		No
Papaioannou, Alexandra	Pharma	Yes	Amgen, Eli Lilly	Yes		No
Wark, John	Ex	Yes	Kyowa Kirin Australia (hypophosphatemia)			Yes

STAKEHOLDER PARTICIPANTS

Associations	Location	Contact
British Columbia Ministry of Health	Vancouver, BC	Sinsha Asuri
Canadian Association of Radiologists	Ottawa, ON	Nick Neuheimer
Canadian Pharmacists Association	Ottawa, ON	Farah Dandachi
Canadian Geriatrics Association	Markham, ON	Leo Lai
Canadian Rheumatology Association	Tecumseh, ON	Claire McGowan
Canadian Society of Endocrinology and Metabolism	Ottawa, ON	Inika Anderson
Dietitians of Canada	Toronto, ON	Dawna Royall

Individuals	Affiliation
Adachi, Jonathan	McMaster University, Hamilton, ON
Atkinson, Stephanie	McMaster University, Hamilton, ON
Bertinato, Jesse	Health Canada
Billington, Emma	University of Calgary, Calgary, AB
Brown, Jacques	University of Laval, Quebec, QC
Gagnon, Claudia	University of Laval, Quebec, QC
Goltzman, David	McGill University, Montreal, QC
Hagan, Shelly	Covenant Health Services, Edmonton, AB
Hanley, David	University of Calgary, Calgary, AB
Jain, Ravi	Ontario Osteoporosis Strategy
Juby, Angela	University of Alberta, Edmonton, AB
Kaiser, Stephanie	Dalhousie University, Halifax, NS
Lau, Adrian	University of Toronto, Toronto, ON
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Weiler, Hope	Health Canada
Whiting, Susan	University of Saskatchewan, Saskatoon, SK
Wong, Andy Kin On	University Health Network, Toronto, ON
Ye, Carrie	University of Alberta, Edmonton, AB
Yeksel, Nese	University of Alberta, Edmonton, AB

OUTCOMES OF INTEREST

Outcomes of interest:

Outcomes	• Hip fractures • Vertebral fractures • All site fractures • Fracture-related mortality • Functionality and disability (includes surrogate measures such as frailty measures or long-term care admission) • Falls and fall-related injuries • Quality of life or wellbeing • Adverse events (serious and minor)

Baseline risks and large vs small benefits/harms:

Background: The GRADE process requires agreement on what constitutes a large versus a trivial absolute difference, for both desirable effects (benefits) and undesirable effects (risks). This will be needed to estimate the magnitude of effects from specific interventions in GRADEpro (shown below as Desirable Effects and Undesirable Effects).

Justification (from GRADE publications): In most instances, one should seriously consider expressing the magnitude of effect as an OR or relative risk as well as a risk difference. The advantages include familiarity for clinicians and ability to apply GRADE guidance for large and very large effects (for relative effect) and usefulness for clinical decision making (for absolute effects). Because presentation of relative effects alone may be misleading, when relative effects are large but absolute effects small, the summary should ensure communication of the magnitude of absolute effect.

This information is also considered to be important by patient-partners.

Process: All 2023 Guideline Update Group members were invited to provide numeric estimates on what would constitute a moderate effect, entered as a number on the "Scoring" sheet, representing judgement.

Values much larger than this moderate effect represent a large benefit/risk = an effect size that would strongly affect recommendations and be clinically meaningful to patients. Values much smaller than this moderate effect represent a small benefit/risk = an effect size that would not affect recommendations or not be clinically meaningful to patients.

We present in the Table below, for each outcome, the baseline risk and what constitutes the moderate change in the estimate. (N=23 Guideline Update group participants who provided data)

Interpretation: The geometric mean (GeoMean) was selected as the primary measure summarizing moderate benefit/risk (also generated arithmetic mean, median, minimum, maximum).

Table Numeric estimates provided by the Guideline Update Group members (N=23) on what constitutes a moderate effect for each outcome of interest

CHANGE IN OUTCOMES FROM INTERVENTION	Baseline with units	Moderate Benefit/Risk (increase or decrease from baseline)				
		Geo Mean	Mean	Median	Min	Max
Reduction in Hip fractures over 10 years (high risk patient)	30 per 1,000 persons	8	9	10	2	21
Reduction in Vertebral fractures over 10 years , clinically diagnosed (high risk patient)	50 per 1,000 persons	14	17	18	3	35
Reduction in Vertebral fractures over 10 years, all including only x-ray diagnosis (high risk patient)	150 per 1,000 persons	41	48	50	10	105
Reduction in All site fractures over 10 years (high risk patient)	300 per 1,000 persons	68	83	100	10	210
Reduction in Death in the first year after a fracture	135 per 1,000 persons	22	29	23	5	100
Reduction in Long-term care admission after hip fracture (functionality and disability)	250 per 1,000 persons	48	59	50	15	175
Reduction in Fallers (1 or more falls in the last year)	200 per 1,000 persons	47	54	50	18	140
Increase in Atypical femur fracture, after >5-8 years bisphosphonate use (serious adverse event)	100 per 100,000 person-yrs	25	40	20	5	200
Increase in Osteonecrosis of the jaw (serious adverse event)	10 per 100,000 person-yrs	5	13	4	1	100
Increase in Drug intolerance leading to stopping medication (minor adverse event)	10%	6	9	6	1	50
		N=23				

OUTCOMES	Baseline source
Reduction in Hip fractures over 10 years (high risk patient)	Defines high risk for NOF guidelines
Reduction in Vertebral fractures over 10 years , clinically diagnosed (high risk patient)	1/4 of High risk for MOF, 20% 10-year
Reduction in Vertebral fractures over 10 years, all including only x-ray diagnosis (high risk patient)	1/3 of all VF are clinical
Reduction in All site fractures over 10 years (high risk patient)	50% more than MOF
Reduction in Death in the first year after a fracture (women)	Morin et al, OSIN. https://www.ncbi.nlm.nih.gov/pubmed/21161507
Reduction in Long-term care admission after hip fracture (functionality and disability)	Morin et al, OSIN https://www.ncbi.nlm.nih.gov/pubmed/22008882
Reduction in Fallers	https://bmcgeriatr.biomedcentral.com/articles/10.1186/1471-2318-14-22
Increase in Atypical femur fracture, long term user (serious adverse event)	JBMR Task Force https://www.ncbi.nlm.nih.gov/pubmed/23712442. Dell et al https://www.ncbi.nlm.nih.gov/pubmed/22836783.
Increase in Osteonecrosis of the jaw (serious adverse event)	Khan https://www.ncbi.nlm.nih.gov/pubmed/25414052
Increase in Drug intolerance leading to stopping medication (minor adverse event)	Average in pivotal trials ALN and RIS

QUESTIONS

Exercise Working Group

Question 1: Should impact exercises vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?

Question 2: Should walking vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?

Question 3: Should progressive resistance training vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?

Question 4: Should yoga vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?

Question 5: Should Pilates vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?

Question 6: Should balance and functional exercises vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?

Question 7: Should exercises targeting back extensor muscles, core stability or posture vs. no intervention be used for men and postmenopausal women aged 50 years and older with hyperkyphosis (87)

Nutrition Working Group

Question 1: Should calcium supplementation versus no supplementation be used in individuals at increased risk of fracture?

Question 2: Should vitamin D supplementation versus no supplementation be used in individuals at increased risk of fracture?

Question 3: Should calcium and vitamin D supplementation versus no supplementation be used in individuals at increased risk of fracture?

Question 4: Should protein supplementation versus no supplementation be used in individuals at increased risk of fracture?

Question 5: Should magnesium supplementation versus no supplementation be used in individuals at increased risk of fracture?

Question 6: Should vitamin K supplementation versus no supplementation be used in individuals at increased risk of fracture?

Fracture Risk Assessment Working Group

Question 1: Which strategy (DXA alone, risk factor score with DXA, and or prior fracture) to identify postmenopausal females and males aged 50 years and older at high risk of osteoporotic fracture for pharmacotherapy will prevent the most fractures?

A. Should a population-based screening strategy using fracture risk vs. targeted case-finding be used for reducing the risk of osteoporotic fracture?
B. Should treatment of high fracture risk vs. another criterion be used for initiating pharmacotherapy to prevent the most osteoporotic fractures?
C. Should a specific fracture risk threshold vs. BMD T-score be used for initiating pharmacotherapy to prevent the most osteoporotic fractures?
D. Should treatment of higher risk subgroups vs. lower risk subgroups be used for initiating pharmacotherapy to prevent the most osteoporotic fractures?

Question 2: Should postmenopausal females and males aged 50 years or older undergo DXA screening (versus no screening) based upon age, OST, fracture risk score without DXA, or prior fracture to identify those at high risk for future fractures for whom anti-fracture therapy has been shown to be effective? Should DXA screening vs. no DXA screening be used for identifying those qualifying for anti-fracture therapy due to high fracture risk based upon age, fracture risk score or another clinical score?

A. Should shorter interval vs. longer interval fracture risk re-assessment be used for case- finding in those who are not initially treatment candidates?
B. Does the FRAX or the Canadian Association of Radiologists-Osteoporosis Canada (CAROC) fracture prediction tool most accurately predict fracture outcomes in individuals age 50 years or older?

Question 3: Should postmenopausal females and males aged 50 years or older without known vertebral fractures receive vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays (versus no spine imaging) to find those with vertebral fractures for whom anti-fracture therapy may be given?

A. Does vertebral imaging predict clinically important fractures?
B. Does vertebral imaging lead to increased use of anti-fracture treatment?
C. Does vertebral imaging lead to reduced risk of fracture due to a change in treatment?

D. For which subgroup(s) does vertebral imaging have the largest effect on treatment? i.e. are there subgroups within the population that particularly benefit from vertebral imaging?

Question 4: Should postmenopausal females and males aged 50 years or older receiving treatment to prevent fractures be monitored with repeat DXA, fracture risk score with DXA (e.g., FRAX, CAROC), bone turnover markers (BTM) versus clinically (no specific testing)?

A. Does monitoring, while on therapy, lead to a change in fracture outcomes within a treated population?
B. Does an observed increase/decrease (vs stability) in the monitoring parameter while on therapy predict a difference in fracture outcomes within a treated population? (only if insufficient data on 4A)
C. Does monitoring while on therapy lead to a change in treatment within a treated population? (only if insufficient data on 4B)

Question 5: Should postmenopausal females and men aged 50 years or older currently on a bisphosphonate interruption (drug holiday) be monitored with repeat DXA, fracture risk score with DXA (e.g., FRAX, CAROC), bone turnover markers (BTM) versus clinically (no specific testing)?

A. Does an observed increase/decrease (vs stability) in the monitoring parameter during the hiatus following bisphosphonate therapy predict a difference in fracture outcomes?
B. Does an observed increase/decrease in the monitoring parameter during the hiatus following bisphosphonate predict a change in treatment? (Only if insufficient data on 5A)

Question 6: Should Fracture Liaison Services (FLS) be recommended to improve post fracture care/ fracture risk reduction versus usual care?

A. Does FLS increase post-fracture treatment initiation?
B. Does FLS increase treatment adherence?
C. Does FLS reduce re-fracture rates?
D. Does FLS reduce mortality rates?
E. Does FLS increase post-fracture BMD Testing?

Pharmacotherapy Working Group

Question 1a: For postmenopausal females and males aged 50 years and older, who are at risk of fractures (*to define*), should pharmacotherapy* be recommended?

Question 1.b: Should one pharmacotherapy agent* vs. another be recommended as the initial treatment choice for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures (*defined by subgroups)*?
*using bisphosphonates (alendronate, risedronate, zoledronic acid, etidronate), denosumab, teriparatide, romosozumab, raloxifene (women only) or estrogen (women only)

Question 2: Should longer duration of oral bisphosphonates versus shorter duration be recommended for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures (defined by subgroups)?

Question 3: Should longer duration of zoledronic acid versus shorter duration be recommended for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures (defined by subgroups)?

Question 4: Should longer duration of denosumab versus shorter duration be recommended for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures (defined by subgroups)?

Question 5: Should a change in pharmacotherapy be recommended when new fracture(s) and/or unexpected bone loss occurs while on effective treatment vs. no change in pharmacotherapy, for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures (defined by subgroups)?

Question 6: Should an alternative medication be recommended after taking denosumab for a specified duration to prevent rapid bone loss and risk of rebound vertebral fractures, for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures (defined by subgroups)?

Question 7: Should anti-resorptive therapy be recommended after taking anabolic therapy (teriparatide or romosozumab) to prevent loss of bone density gains for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures?

Question 8: Should an evaluation to rule out secondary causes of osteoporosis (minimum biochemistry) be recommended prior to the initiation of pharmacotherapy, for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures (*define by subgroups and pharmacotherapy agent)*? (Good practise statement – no search performed)

Question 9: Should regular assessment of treatment adherence and appropriateness of pharmacotherapy be recommended (particularly when ongoing fractures or unexpected bone loss while on effective therapy), for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures? (Good practise statement – no search performed)

Question 10: Should referral to an osteoporosis specialist be recommended when there are concerns of possible secondary causes of osteoporosis, inadequate response to pharmacotherapy, co-morbidities that complicate management (eg. advanced renal impairment), atypical femoral fractures or osteonecrosis of the jaw, or uncertainty regarding appropriate treatment duration, for postmenopausal females and males aged 50 years and older, who are at risk of osteoporotic fractures? (Good practise statement – no search performed)

Question 11: Should counselling and monitoring for atypical femoral fracture and osteonecrosis of the jaw be recommended for postmenopausal females and males aged 50 and older, who are on bisphosphonate or denosumab therapy? (Good practise statement – no search performed)

Question 12: When initiating pharmacotherapy, should pre-treatment with adequate vitamin D and calcium intake be recommended? (Good practise statement – no search performed)

SEARCH STRATEGIES

Exercise Working Group

Search strategy used for questions 1-6:
A librarian with experience conducting systematic reviews developed a common literature search and used a deduplication process to identify studies for the first six types of exercise interventions to be considered in the guidelines. The search was conducted in MEDLINE (Ovid), EMBASE (Ovid), Cochrane CENTRAL (clinical trials), Cochrane database of systematic reviews (meta-analyses), CINAHL (allied health journal content), Epistemonikos, and Web of Science in August 2018 and updated in December 2020. Search terms consisted of a combination of subject headings (i.e., MeSH) and author keywords related to interventions used in the prevention and treatment of osteoporosis in older adults. The full search strategy can be found in appendices from the published systematic reviews. No restrictions were placed on gender, ethnicity, exercise setting, country of origin, or language; however, only human studies written in English, Portuguese, Spanish, Italian, or Farsi were included due to language limitations of the working group. Randomized controlled trials (RCTs) and quasi-randomized controlled trials comparing exercise to placebo, attention control, or non-physical activity interventions were included for questions 1-3, 6 and 7. For Questions 4 and 5 we also included cohort studies, case-control studies, cross-sectional studies and case reports were considered for inclusion in the systematic review to ensure that all available studies of Pilates or yoga interventions were captured. We included non-randomized trials for yoga and Pilates because we hypothesized that there would be a limited number of RCTs, and we wanted to capture all available evidence for each outcome. Editorials and opinion pieces were excluded. Studies were included if the intervention lasted at least 4 weeks. We included studies of men or postmenopausal women with a mean age of 50 years or older with either a) low bone mineral density (BMD) at the femoral neck or lumbar spine (T-score ≤ –1.00), measured with dual-energy X-ray absorptiometry (DXA); b) history of ≥1 fragility fracture (i.e., fracture of the spine, hip, wrist, humerus); or c) moderate or high-risk of fragility fracture based on the CAROC (Siminoski et al. 2007), FRAX (Kanis et al. 2009), or GARVAN (Nguyen et al. 2008) calculators. Studies of individuals with secondary osteoporosis, glucocorticoid-induced osteoporosis, or pathological fractures were excluded. Studies of older adults were only included if a subgroup analysis was conducted in individuals with low bone mass, or ≥80% of participants had low bone mass. If it was unclear whether studies met inclusion criteria, authors were contacted. Interventions could be home- or centre-based, individual or group-based, and either supervised or unsupervised. Studies combining exercise with pharmacological or other co-interventions (excluding whole-body vibration) were included unless unevenly administered to the intervention and control groups. Studies were included if at least 1 comparator group received either no intervention, placebo, a non-exercise or non-physical therapy intervention (e.g., educational intervention), or an attention control not expected to affect outcomes of interest. Systematic reviews were conducted for each type of exercise, and the definitions of each type are listed in published reviews or are available on request. When there was insufficient evidence for the effect of a type of exercise on one of our outcomes, we did an Epistemonikos search for systematic reviews of that type of exercise in older adults, as indirect evidence. References were stored and managed using EndNote (https://www.myendnoteweb.com/Clarivate Analytics, Philadelphia, PA, USA). Titles and abstracts were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) for screening and data extraction.

Search strategy for question 7:
The literature search was conducted in the following databases: MEDLINE (Ovid), EMBASE (Ovid), Cochrane CENTRAL (clinical trial), Cochrane database of systematic reviews (meta-analyses), CINAHL (allied health journal content), Web of Science, and no restrictions by language were applied at this stage. Medical Subject Headings (MeSH terms) and keywords associated with kyphosis, posture, and exercise interventions were used to design the search strategy. The literature search was performed in May 2020. The full search strategy is reported in in the published systematic review.

Selection criteria related to study design, population, intervention, comparator, outcome, and time are listed below. Based on our experience conducting a similar review in 2014, [24] we were not expecting to retrieve a large number of randomized controlled trials (RCTs) and quasi-RCTs. Therefore, in addition to RCTs and quasi-RCTs, we included pre-post design studies, cohort studies, and case–control studies to provide a comprehensive understanding of the research in this area. Only RCTs and quasi-RCTs were included in meta-analyses. Full texts published in English or Italian were screened, because members of the research team could speak those languages fluently. We included studies on men and women aged 45 years or older with hyperkyphosis, defined as a thoracic spine curvature of 40° or more measured with any validated tools. To be consistent with our prior review, we decided to make our criteria less restrictive so that we might capture more studies and make inferences with higher certainty. Therefore, we expanded the inclusion criteria to studies that did not specify how hyperkyphosis was measured but described their participants as having a flexed posture at baseline, or that had at least one group with a mean kyphosis angle of at least 40° at the baseline. We considered sensitivity analyses in studies of individuals with low bone mass or vertebral fractures to determine if the effects varied by population. We included any exercise interventions or physical therapy that involved at least one active component performed independently by the participants, to distinguish active exercise from passive mobilization aided by a physical therapist. We included in the meta-analysis studies that had at least one comparator group that received no intervention or a non-exercise or a non-physical therapy intervention (e.g., educational intervention). Studies were included if the intervention lasted at least 4 weeks. References were stored and managed using EndNote (https://www.myendnoteweb.com/Clarivate Analytics, Philadelphia, PA, USA). Titles and abstracts were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) for screening and data extraction.

PubMed search strategy
#1 exercise [mesh] OR exercis* [tiab] OR yoga [tiab] OR pilates [tiab] OR “exercise therap*” [tiab] OR “physical activit*” [tiab] OR “exercise movement techniques” [tiab] OR “resistance training” [tiab] OR “weight lifting” [mesh] OR “exercise therapy” [mesh] OR “exercise movement techniques” [mesh] OR “physical fitness” [MeSH] OR lifting effort[tiab] OR stretching[tiab] OR swimming[tiab]
#2 posture [tiab] OR “spinal curvature” [tiab] OR “hyperkypho*” [tiab] OR kypho* [tiab] OR “skeletal alignment” [tiab] OR “kyphosis” [mesh]
#3 “elderly” [tiab] OR “older adult*” [tiab] OR senior* [tiab] OR “older people” [tiab] OR “middle age*” [tiab] OR “aged” [mesh] OR “middle aged” [mesh] OR old age[tiab] OR geriatric* [tiab]
Final Search: #1 AND #2 AND #3

MEDLINE search strategy
1 osteopor* or osteopenia or low bone density or low bone mineral density or low bone mass or bone loss* or bone remodel$ing).ti,ab,kw.

2 ((fragility or spine or spinal or vertebra* or hip* or femoral neck or compression) adj2 fracture*).ti,ab,kw.

3 exp osteoporosis/ or bone density/ or exp bone remodeling/ or exp hip fractures/ or spinal fractures/ or fractures, compression/ or osteoporotic fractures/

4 1 or 2 or 3

5 (older or elder or elderly or frail or senior* or middle age* or geriatric).ti,ab,kw.

6 middle aged/ or exp aged/

7 5 or 6

8 (Exercis* or Physical activit* or Physical fitness or Weight bearing or Load bearing or Axial bearing or Running or Dancing or Stair climb* or treadmill* or walk or walking or weight lifting or yoga or pilates).ti,ab,kw.

9 ((Resistance or strength or strengthening or weight or high impact) adj2 (train* or exercis*)).ti,ab,kw.

10 (Balance adj2 (exercis* or train*)).ti,ab,kw.

11 exp exercise/ or exp sport/ or dancing/ or dance therapy/ or exp exercise therapy/ or weight bearing/ or osteoporosis/rh or walking/ or plyometric exercise/ or resistance training/ or yoga/ or postural balance/

12 8 or 9 or 10 or 11

13 (Meta analys* or metaanalys*).ti,ab,kw.

14 ((Systematic or methodologi*) adj5 (review* or overview*)).ti,ab,kw.

15 (Cochrane or Embase or Psyclit or Psychlit or Medline or pubmed).ab.

16 (quantitativ* adj5 synthesi*).ti,ab,kw.

17 ((pooled or pooling) and analys*).ti,ab,kw.

18 (randomized controlled trial* or Randomised controlled trial* or rct or clinical trial* or (allocated adj2 random*)).ti,ab,kw.

19 Randomized controlled Trials as Topic/ or Randomized controlled trial/ or Random allocation/ or Double blind method/ or single blind method/ or exp Clinical trial/ or exp clinical trials as topic/

20 13 or 14 or 15 or 16 or 17 or 18 or 19

21 4 and 7 and 12 and 20

22 exp animals/ not humans/

23 21 not 22

24 23 not (case reports or letter or editorial or comment).pt.

EMBASE search strategy

26 (osteopor* or osteopenia or low bone density or low bone mineral density or low bone mass or bone loss* or bone remodel$ing).ti,ab,kw.

27 ((fragility or spine or spinal or vertebra* or hip* or femoral neck or compression) adj2 fracture*).ti,ab,kw.

28 exp osteoporosis/ or osteopenia/ or bone density/ or bone remodeling/ or bone atrophy/ or bone demineralization/ or fragility fracture/ or exp spine fracture/ or exp hip fracture/

29 26 or 27 or 28

30 (older or elder or elderly or frail or senior* or middle age* or geriatric).ti,ab,kw. middle aged/ or exp aged/

31 30 or 31

32 (Exercis* or Physical activit* or Physical fitness or Weight bearing or Load bearing or Axial bearing or Running or Dancing or Stair climb* or treadmill* or walk or walking or weight lifting or yoga or pilates).ti,ab,kw.

33 ((Resistance or strength or strengthening or weight or high impact) adj2 (train* or exercis*)).ti,ab,kw.

34 (Balance adj2 (exercis* or train*)).ti,ab,kw.

35 exp exercise/ or exp sport/ or dancing/ or dance therapy/ or exp kinesiotherapy/ or weight bearing/ or osteoporosis/rh or walking/ or plyometrics/ or resistance training/ or yoga/ or pilates/ or body equilibrium/

36 33 or 34 or 35 or 36

37 (Meta analys* or metaanalys*).ti,ab,kw.

38 ((Systematic or methodologi*) adj5 (review* or overview*)).ti,ab,kw.

39 (Cochrane or Embase or Psyclit or Psychlit or Medline or pubmed).ab.

40 (quantitativ* adj5 synthesi*).ti,ab,kw.

41 ((pooled or pooling) and analys*).ti,ab,kw.

42 exp meta analysis/ or systematic review/

43 (randomized controlled trial* or Randomised controlled trial* or rct or clinical trial*).ti,ab,kw.

44 (allocated adj2 random*).ti,ab,kw.

45 randomized controlled trial/ or exp randomization/ or random allocation/ or double blind method/ or single blind method/ or exp clinical trial/ or exp clinical trials as topic/

46 38 or 39 or 40 or 41 or 42 or 43 or 44 or 46

47 29 and 32 and 37 and 47

48 (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) and (human/ or normal human/ or human cell/)

49 (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not 49

50 48 not 50

51 51 not (case study/ or letter/ or abstract report/ or editorial.pt. or note.pt.)

CINAHL search strategy

S18 S13 AND S14 AND S15 AND S16
Limiters – Peer reviewed

S17 S13 AND S14 AND S15 AND S16

S16 ((MH "Meta Analysis") OR (MH "Systematic Review")) OR TX (meta analy* OR metaanaly*) OR TX ((systematic or methodologi*) N5 (review or overview)) OR AB (Cochrane or Embase or Psyclit or Psychlit or Medline or pubmed) OR TX quantitativ* N5 synthesi* OR TX ((pooled or pooling) and analys*) OR TX (randomized controlled trial* or randomised controlled trial* or rct) OR TX (allocat* random* OR placebo* OR random* allocate* OR randomi* control* trial*) OR TX clinical N1 trial* OR ((MH "random assignment") OR (MH "clinical trials+"))

S15 ((MH "Exercise+") OR (MH "Sports+") OR (MH "Dancing+") OR (MH "Dance Therapy") OR (MH "Therapeutic Exercise+") OR (MH "Weight-Bearing") OR (MH "Walking+") OR (MH "Resistance Training") OR (MH "Muscle Strengthening+") OR (MH "yoga") OR (MH "pilates") OR (MH "balance training, physical") OR (MH "balance, postural")) OR TX (

Exercis* or Physical activit* or Physical fitness or Weight bearing or Load bearing or Axial bearing or Running or Dancing or Stair climb* or treadmill* or walk or walking or weight lifting or yoga or pilates) OR TX ((Resistance or strength or strengthening or weight or “high impact”) N2 (train* or exercis*)) OR TX (Balance adj2 (exercis* or train*))

S14 ((MH "Middle Age") OR (MH "Aged+") OR (MH "Aging") OR (MH "Rehabilitation, Geriatric")) OR TX (older or elder or elderly or frail or senior* or middle age* or geriatric or "old age")

S13 (MH "Osteoporosis+") OR (MH "Bone Density") OR (MH "Bone Remodeling+") OR (MH "hip fractures+") OR (MH spinal fractures+") OR TX (osteopor* or osteopenia or low bone density or low bone mineral density or low bone mass or bone loss* or bone remodeling or bone remodelling) OR TX ((fragility or spine or spinal or vertebra* or hip* or femoral neck or compression) N2 fracture*)

Web of Science search strategy

#6 #4 AND #3 AND #2 AND #1
Refined by: DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2018

#5 #4 AND #3 AND #2 AND #1
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2018

#4 TS=("Meta analys*" or "metaanalys*") OR TS=("systematic" NEAR/2 ("review" or "overview")) OR TS=(("pooled" OR "pooling") AND "analys*") OR TS=("randomized controlled trial*" OR "randomised controlled trial*" OR "rct" OR "clinical trial*" OR "random allocat*")
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2018

#3 TS=("Exercis*" or "Physical activit*" or "Physical fitness" or "Weight bearing" or "Load bearing" or "Axial bearing" or "Running" or "Dancing" or "Stair climb*" or "treadmill*" or "walk" or "walking" or "weight lifting" or "yoga" or "pilates") OR TS=(("Resistance" or "strength" or "strengthening" or "weight" OR "high impact") NEAR/2 (train* or exercis*)) OR TS=(Balance NEAR/2 (exercis* or train*))

#2 TS=("older" OR "elder" or "elderly" or "frail" or "senior*" or "middle age*" or "geriatric")
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2018

#1 TS=("osteopor*" or "osteopenia" or ("low" NEAR/2 ("bone density" OR "bone mineral density" or "bone mass")) or bone loss* or "bone remodeling" or "bone remodeling") OR TS=(("fragility" OR "spine" OR "spinal" OR "vertebra*" or "hip" OR "compression") NEAR/2 "fracture*")
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2018

Cochrane Library search strategy

low #1 ((fragility or	osteopor* or osteopenia or low bone density or low bone mineral density or bone mass or bone loss* or bone remodeling or bone remodeling or spine OR spinal OR vertebra* or hip* or femoral) NEAR/2 fracture*)
#2	MeSH descriptor: [Osteoporosis] explode all trees
#3	MeSH descriptor: [Bone Density] explode all trees
#4	MeSH descriptor: [Bone Remodeling] explode all
trees #5	MeSH descriptor: [Hip Fractures] explode all trees
#6	MeSH descriptor: [Spinal Fractures] explode all trees
#7	MeSH descriptor: [Fractures, Compression] explode all
trees #8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	older or old or elder or elderly or frail or senior* or middle age* or
geriatric #10	MeSH descriptor: [Middle Aged] explode all trees
#11	MeSH descriptor: [Aged] explode all trees
#12	#9 OR #10 OR #11
#13	Exercis* or Physical activit* or Physical fitness or Weight bearing or Load bearing or Axial bearing or Running or Dancing or Stair climb* or treadmill* or walk or walking or ((Resistance or strength or strengthening or weight) NEAR/2 (train* or exercise*)) or weight lifting or yoga or pilates or (Balance NEAR/2 (exercis* or train*))
#14	MeSH descriptor: [Exercise] explode all
trees #15	MeSH descriptor: [Sports] explode all
trees	

#16	MeSH descriptor: [Dance Therapy] explode all
trees #17	MeSH descriptor: [Dancing] explode all trees
#18	MeSH descriptor: [Exercise Therapy] explode all
trees #19	MeSH descriptor: [Weight-Bearing] explode all
trees #20	MeSH descriptor: [Walking] explode all trees
#21	MeSH descriptor: [Resistance Training] explode all
trees #22	MeSH descriptor: [Yoga] explode all trees
#23	MeSH descriptor: [Postural Balance] explode all trees
#24	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#8 AND #12 AND #24

Epistemonikos search strategy

(title:(osteopor* OR osteopenia OR low bone density OR low bone mineral density OR low bone mass OR bone loss* OR bone remodeling OR bone remodeling OR ((fragility OR spine OR spinal OR

vertebra* OR hip* OR femoral OR compression) AND fracture*)) OR abstract:(osteopor* OR osteopenia OR low bone density OR low bone mineral density OR low bone mass OR bone loss* OR bone remodeling OR bone remodeling OR ((fragility OR spine OR spinal OR vertebra* OR hip* OR femoral OR compression) AND fracture*)))

AND

(title:((older OR old OR elder OR elderly OR frail OR senior* OR middle age* OR geriatric)) OR abstract:((older OR old OR elder OR elderly OR frail OR senior* OR middle age* OR geriatric)))

AND

(title:(Exercis* OR Physical activit* OR Physical fitness OR Weight bearing OR Load bearing OR Axial bearing OR Running OR Dancing OR Stair climb* OR treadmill* OR walk OR walking OR ((Resistance OR strength OR strengthening OR weight) AND (train* OR exercise*)) OR weight lifting OR yoga OR pilates OR (Balance AND (exercis* OR train*))) OR abstract:(Exercis* OR Physical activit* OR Physical fitness OR Weight bearing OR Load bearing OR Axial bearing OR Running OR Dancing OR Stair climb* OR treadmill* OR walk OR walking OR ((Resistance OR strength OR strengthening OR weight) AND (train* OR exercise*)) OR weight lifting OR yoga OR pilates OR (Balance AND (exercis* OR train*))))

Search strategy for systematic review of exercise in people with hyperkyphosis

PubMed

#1 exercise [mesh] OR exercis* [tiab] OR yoga [tiab] OR pilates [tiab] OR “exercise therap*” [tiab] OR “physical activit*” [tiab] OR “exercise movement techniques” [tiab] OR “resistance training” [tiab] OR “weight lifting” [mesh] OR “exercise therapy” [mesh] OR “exercise movement techniques” [mesh] OR “physical fitness” [MeSH] OR lifting effort[tiab] OR stretching[tiab] OR swimming[tiab]

#2 posture [tiab] OR “spinal curvature” [tiab] OR “hyperkypho*” [tiab] OR kypho* [tiab] OR “skeletal alignment” [tiab] OR “kyphosis” [mesh]

#3 “elderly” [tiab] OR “older adult*” [tiab] OR senior* [tiab] OR “older people” [tiab] OR “middle age*” [tiab] OR “aged” [mesh] OR “middle aged” [mesh] OR old age[tiab] OR geriatric* [tiab]

Final Search: #1 AND #2 AND #3

Cumulative Index to Nursing and Allied Health Literature Search

#1 MH (“exercise” OR “therapeutic exercise”) OR TX (exercis* OR pilates OR yoga OR “physical activit*” OR “exercise movement techniques” OR “resistance training” OR “weight lifting” OR lifting effort OR stretching OR swimming)

#2 TX posture OR “spinal curvature” OR hyperkypho* OR kypho* OR “skeletal alignment”

#3 MH (“aged” OR “middle age” OR “frail elderly”) OR TX (elderly OR “older adult*” OR “old age” OR “older people” OR senior* OR “middle age*” OR geriatric*)

Final Search: S1 AND S2 AND S3

Embase search

#1 kyphosis/

#2 posture.tw

#3 spinal curvature.tw

#4 skeletal alignment.tw

#5 hyperkypho*.tw

OR kypho*.tw

#6 1 or 2 or 3 or 4 or 5

#7 exercise/ or aerobic exercise/ or anaerobic exercise/ or aquatic exercise/ or arm exercise/ or breathing exercise/ or dynamic exercise/ or endurance training/ or isokinetic exercise/ or muscle exercise/ or pilates/ or plyometrics/ or resistance training/ or static exercise/

#8 exercis*.tw

#9 physical activity/ or lifting effort/ or stretching/ or swimming/ or weight lifting/

OR resistance training.tw OR weight lifting.tw OR physical fitness.tw OR lifting effort.tw OR stretching.tw OR swimming.tw

#10 yoga.tw

#11 7 or 8 or 9 or 10

#12 aged/

#13 older adult*.tw

#14 middle aged/

#15 senior*.tw

OR elderly.tw OR older people.tw OR middle age*.tw OR old age.tw OR geriatric*.tw

#16 12 or 13 or 14 or 15

Final Search: #6 and #11 and #16

Cochrane search

#1 Exercis* or “Physical activit*” or “Physical fitness” or ((Resistance or strength or strengthening or weight) NEAR/2 (train*)) or “weight lifting” or yoga or pilates or (Balance NEAR/2 (train*)) OR “lifting effort” OR stretching OR swimming

#2 MeSH descriptor: [Exercise] explode all trees
#3 MeSH descriptor: [Yoga] explode all trees
#4 MeSH descriptor: [Exercise Therapy] explode all trees
#5 MeSH descriptor: [Exercise movement techniques] explode all trees
#6 MeSH descriptor: [Resistance Training] explode all trees
#7 MeSH descriptor: [Weight Lifting] explode all trees
#8 MeSH descriptor: [Physical Fitness] explode all trees

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#9 postur* or “spinal curvature*” or hyperkypho* or kypho* or “skeletal alignment”

#10 MeSH descriptor: [Posture] explode all trees

#11 MeSH descriptor: [Spinal Curvatures] explode all trees

#12 MeSH descriptor: [Kyphosis] explode all trees

#13 #9 OR #10 OR #11 OR #12

#14 “older adult*” OR “older people” or “old age” or elder* or frail or senior* or “middle age*” or geriatric*

#15 MeSH descriptor: [Middle Aged] explode all trees

#16 MeSH descriptor: [Aged] explode all trees

#17 #14 OR #15 OR #16

#18 #12 AND #13 AND 17

Web of Science

#1 TS=(postur* or “spinal curvature*” or hyperkypho* or kypho* or “skeletal alignment”)

#2 TS=(“older adult*” or elder* or “older people” or “old age” or frail or senior* or “middle age*” or geriatric*)
Indexes=SCI-EXPANDED
# 3 TS=(Exercis* or “Physical activit*” or “Physical fitness” or “weight lifting” or yoga or pilates or “lifting effort” or stretching OR swimming) or TS=((Resistance or strength or strengthening or weight) NEAR/2 (train*)) or TS=(Balance NEAR/2 (train*))

#5 #1 AND #2 AND #3
Indexes=SCI-EXPANDED

Recent systematic reviews on each nutrient of interest (calcium, vitamin D, protein, magnesium, vitamin K) and bone health were searched using the Epistemonikos database. This was performed by William Gittings (WG) and Wendy Ward (WEW). Recent was defined as systematic reviews published within the previous 5 years. Searches were conducted separately, by nutrient of interest, in combination with each of the following terms: osteoporosis, fracture and bone mineral density.

Questions 1 -4: Multiple systematic reviews for calcium, vitamin D and protein were identified and subsequently screened for relevance to the research questions using PICO criteria and for risk of bias using the ROBIS tool (WG, WEW). All Nutrition Working Group members reviewed the lists of systematic reviews and provided feedback. Together, members decided on which systematic reviews would be of highest priority for each of the 5 outcomes in the Evidence to Decision tables (i.e. fracture, BMD, falls, quality of life, adverse effects). This was based on quality of the systematic review as well as alignment with PICO criteria.

Because there were no appropriate systematic reviews identified for magnesium (Question 5) and vitamin K (Question 6) and the outcomes of interest, two searches were done by Cathy Yuan, Librarian at McMaster University.

The searches are shown below:

Questions 5: Magnesium and osteoporosis from 2015 to December 2018

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase <1974 to 2018 December 12>, EBM Reviews - Cochrane Central Register of Controlled Trials <November 2018>
Search Strategy:
---
1 exp *Osteoporosis/ (95830)
2 (osteoporosis or osteoporoses).tw. (158541)
3 exp *Fractures, Bone/ or exp *fracture/ (283053)
4 ((bone* or hip) adj5 (fracture or fractures)).tw. (110350)
5 exp *Bone Density/ (47621)
6 ((bone adj2 density) or BMD).tw. (136553)
7 (fall or falling or falls).tw. (370641)
8 or/1-7 (895714)
9 exp Magnesium/ (135456)
10 exp magnesium intake/ (369)
11 magnesium.mp. (251542)
12 or/9-11 (251542)
13 8 and 12 (5197)
14 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or

aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4043421)
15 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10300856)
16 case report/ or case reports/ or case report.ti. (4293412)
17 conference abstract.pt. or Congresses as Topic/ or Conference Review.pt. or "Journal: Conference Abstract".pt. (3478988)
18 note/ or editorial/ or letter/ or Comment/ or news/ or opinion/ (4202249)
19 (editorial or letter or note).pt. (3871846)
20 or/14-19 (23894174)
21 13 not 20 (2997)
22 limit 21 to yr="2015 -Current" (472)
23 remove duplicates from 22 (338)

****

Question 6: Vitamin K and osteoporosis from 2010 to December 2018

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase <1974 to 2018 December 12>, EBM Reviews - Cochrane Central Register of Controlled Trials <November 2018>
Search Strategy:
---
1 exp *Osteoporosis/ (95830)
2 (osteoporosis or osteoporoses).tw. (158541)
3 exp *Fractures, Bone/ or exp *fracture/ (283053)
4 ((bone* or hip) adj5 (fracture or fractures)).tw. (110350)
5 exp *Bone Density/ (47621)
6 ((bone adj2 density) or BMD).tw. (136553)
7 (fall or falling or falls).tw. (370641)
8 or/1-7 (895714)
9 exp Vitamin K/ (42291)
10 exp vitamin K group/ (25790)
11 vitamin K*.mp. (55745)
12 (aquamephyton* or davitamon k or kanarit or kanavit or kaywan or konakion or mephyton or mono kay or phyllochinon* or phylloquinon* or phytomenadion* or phytonadion* or phytylmenadion* or menadion* or menaquinon* or vacasol or vikasol).tw,kw. (17042)
13 or/9-12 (70232)
14 8 and 13 (2838)
15 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4043421)

16 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10300856)
17 case report/ or case reports/ or case report.ti. (4293412)
18 conference abstract.pt. or Congresses as Topic/ or Conference Review.pt. or "Journal: Conference Abstract".pt. (3478988)
19 note/ or editorial/ or letter/ or Comment/ or news/ or opinion/ (4202249)
20 (editorial or letter or note).pt. (3871846)
21 or/15-20 (23894174)
22 14 not 21 (2035)
23 limit 22 to yr="2010 -Current" (858)
24 remove duplicates from 23 (557)

****

Questions 1, 2 a, b, 4 and 5

The searches were conducted in the following databases: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase <1974 to 2019 January 18>, EBM Reviews - Cochrane Central Register of Controlled Trials <December 2018> to January 2019 and updated to August 15th 2019.

For Questions 4 and 5, one final search was conducted in June 2020 and retrieved no additional publications.

Search Strategy: ----------

1 exp *Osteoporosis/ (96089)

2 (osteoporosis or osteoporoses).ti. (60563)

3 exp *Fractures, Bone/ or exp *fracture/ (284181)

4 (fracture or fractures).ti. (263405)

5 exp *Bone Density/ (47769)

6 (bone density or bone mineral density).ti. (35233)

7 or/1-6 (466508)

8 (Dual-energy X-ray absorptiometr* or DXA or DEXA).tw. (69648)

9 (fracture* risk adj2 (score* or tool* or scale* or calculator* or assessment*)).tw. (3147)

10 (FRAX or CAROC).tw. (4088)

11 Garvan.tw. (144)

12 ((bone adj3 (marker* or biomarker*)) or BTM).tw. (38356)

13 (telopeptide or amino-terminal collagen crosslink* or "NTX" or bone-specific alkaline phosphatase or "BAP" or "BSAP" or procollagen type 1 N-terminal propeptide or "P1NP" or procollagen Type 1 intact N terminal propeptide or "PINP").tw. (34619)

14 or/8-13 (126566)

15 7 and 14 (46687)

16 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or

infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4060787)

17 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10336979)

18 case report/ or case reports/ or case report.ti. (4310361)

19 conference abstract.pt. or Congresses as Topic/ or Conference Review.pt. or "Journal: Conference Abstract".pt. (3507179)

20 note/ or editorial/ or letter/ or Comment/ or news/ or opinion/ (4222925)

21 (editorial or letter or note).pt. (3890178)

22 or/16-21 (24000165)

23 15 not 22 (32388)

24 limit 23 to yr="2000 -Current" (27395)

25 monitor*.tw. (1764716)

26 ((change* or continu* or discontinu* or holiday or hiatus or respon*) adj5 (therap* or treatment* or bisphosphonate* or Alendronate or Risedronate or ibandronate or zoledron* or estrogen* or denosumab or teriparatide* or hormone)).tw. (1199687)

27 25 or 26 (2871052)

28 24 and 27 (3314)

29 remove duplicates from 28 (1842) (January 2019)

+ 192 citations (August 15, 2019)

Question 2c. FRAX vs CAROC

Medline and Embase

1 Caroc.mp

2 Frax.mp

3 1 and 2

4 “Canadian Association of Radiologists and Osteoporosis Canada”.mp.

5 “Canadian Association Radiologists Osteoporosis”.mp.

6 Canad*.mp.

7 exp Association/ or Association.mp.

8 Radiologists.mp. or exp Radiologists/

9 exp Osteoporosis/ or Osteoporosis.mp.

10 exp Risk/ or Risk.mp.

11 Assessment.mp.

12 6 and 7 and 8 and 9 and 10 and 11

13 1 or 12

CIHAHL and Pub Med

1 CAROC

2 FRAX

Question 3: Vertebral Imaging

Database: Embase <1974 to 2019 March 01>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials <January 2019>

Search Strategy:

1 exp Osteoporosis/ (176012)

2 (osteoporosis or osteoporoses).ti. (60790)

3 exp Fractures, Bone/ or exp fracture/ (438663)

4 (fracture or fractures).ti. (263856)

5 Bone Density/ (139497)

6 (bone density or bone mineral density).ti. (35343)

7 or/1-6 (680462)

8 (vertebral fracture assessment or VFA).tw. (8267)

9 ((vertebral or spine or spinal) adj3 (imag* or x-ray* or radiograph*)).tw. (25742)

10 or/8-9 (33708)

11 7 and 10 (6523)

12 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4069418)

13 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10364448)

14 case report/ or case reports/ or case report.ti. (4336550)

15 conference abstract.pt. or Congresses as Topic/ or Conference Review.pt. or "Journal: Conference Abstract".pt. (3537971)

16 note/ or editorial/ or letter/ or Comment/ or news/ or opinion/ (4220570)

17 (editorial or letter or note).pt. (3886422)

18 or/12-17 (24084684)

19 11 not 18 (4373)

20 remove duplicates from 19 (2580)

****

Question 6: Fraction Liaison Services

Medline

1 exp osteoporosis/

2 osteoporotic fractures/

3 osteoporo*.mp,kw,jw.

4 (bone* adj5 (lost or loss* or lose or losing)).mp.

5 (bone* adj10 (postmenopaus* or post-menopaus* or menopaus*)).mp.

6 (bone* adj5 (break* or broke*)).ti,ab.

7 or/1-6

8 (liaison adj5 (service* or program*)).mp.

9 (fracture adj5 (liaison or prevent*)).mp.

10 secondary fracture prevention.mp.

11 ((program* or strateg* or intervention*) adj10 implement*).mp.

12 or/8-11

13 7 and 12

14 (nonhuman/ or animal/ or animal experiment/) not human/

15 13 not 14

16 limit 15 to yr="1999 - Current"

EMBASE

1 exp osteoporosis/

2 fragility fracture/

3 osteoporo*.mp,jx.

4 (bone* adj5 (lost or loss* or lose or losing)).mp.

5 (bone* adj10 (postmenopaus* or post-menopaus* or menopaus*)).mp.

6 (bone* adj5 (break* or broke*)).ti,ab.

7 ((bone*1 adj5 fragil*) or (bone* adj5 (lost or loss* or lose or losing)) or osteoporo* or fractur*).ti,ab.

8 exp fracture/

9 or/1-8

10 (liaison adj5 (service* or program*)).mp.

11 (fracture adj5 (liaison or prevent*)).mp.

12 secondary fracture prevention.mp.

13 ((program* or strateg* or intervention*) adj10 implementa*).mp.

14 or/10-13

15 9 and 14

16 (nonhuman/ or animal/ or animal experiment/) not human/

17 15 not 16

18 limit 17 to yr="1999-Current"

Cochrane

1 MeSH descriptor: [Osteoporosis] explode all trees

2 Osteoporosis

3 Post-Traumatic Osteoporosis

4 Age-Related Osteoporosis

5 Senile Osteoporosis

6 Osteoporosis

7 Osteoporotic Fracture$

8 MeSH descriptor: [Osteoporosis, Postmenopausal] explode all trees

9	Postmenopausal Bone Loss
10	Post-Menopausal Bone Loss
11	Post-Menopausal Bone Loss
12	Postmenopausal Osteoporos$
13	Post-menopausal Osteoporos$
14	Post-menopausal Osteoporos$
15	Osteoporotic Fracture$
16	bone fragility
17	MeSH descriptor: [Fractures, Bone] explode all trees
18	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19	Liaison
20	FLS
21	fracture liaison service
22	fracture liaison services
23	fracture prevention program
24	fracture prevention programs
25	fracture prevention program
26	secondary fracture prevention
27	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
28	#18 and #27

We searched for systematic reviews in Epistemonikos (https://www.epistemonikos.org/) up to December 2020, and reviewed reference lists of relevant reviews. We conducted a broad search including terms for osteoporosis and fracture to capture all pharmacotherapy questions, including reviews of randomised controlled trials for treatment effects, and non-randomised and observational studies for harms and other criteria (such as patient values and preferences and acceptability). We did not use terms for the treatments and limited the search to the last 10 years. One person screened through those reviews and included reviews by balancing recency of the search, quality of the review (using AMSTAR criteria), use of the GRADE approach to assess the evidence, and access to evidence tables. Primary studies included in relevant reviews were also screened for inclusion.

Retracted articles

We are aware of highly cited osteoporosis studies that have been retracted from authors Dr. Yoshihiro Sato, Dr. Jun Iwamoto, Dr. SA Jamal. Along with these studies we searched for other studies using 'retraction' AND osteoporosis in PubMed and did not find additional citations. We explored whether any study from the Japanese group associated with Sato or Iwamoto were included (of which there could be 33 studies). Of those studies, two were included in the network meta-analysis (Barrionuevo 2019) used for estimating the effects of the various medications. Given that these studies amount to 741 people out of almost 200 000 people included in the network, those studies would very likely have little effect on the results and therefore we have chosen not to redo the entire systematic review and analyses. (Avenell, A et al. 2019. An investigation into the impact and implications of published papers from retracted research: systematic search of affected literature. BMJ Open).

EVIDENCE TO DECISION TABLES

Exercise Working Group

QUESTION 1: SHOULD IMPACT EXERCISES VS. NO INTERVENTION BE USED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER AT INCREASED RISK OF FRACTURE?

Should impact exercises vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?	
POPULATION:	Postmenopausal females and males aged 50 years and older at increased risk of fracture
INTERVENTION:	impact exercises
COMPARISON:	no intervention
MAIN OUTCOMES:	Health Related Quality of Life; Physical functioning; Number of Falls; Femoral neck BMD (surrogate for hip fracture); Fragility Fractures; Serious Adverse Events; Minor Adverse Events; All-Cause Mortality;
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	We are updating the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada (section on exercise) as well as the Too Fit to Fracture Recommendations.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low bone strength can increase the risk of bone fractures. One in three women and one in five men over the age of 50 will experience a fracture due to low bone strength. Fractures can cause pain or impaired mobility. People who have hip or vertebral fractures are more likely to die prematurely, often as a result of fracture-related complications. Exercise is often recommended to reduce fracture risk, but there are many types of exercise, and some types may have more benefits when it comes to health or quality of life than others. Moreover, patients, exercise professionals and health care providers may be concerned about the potential for harms with some types of exercise. Patients should be encouraged to perform regular physical activities that they enjoy for overall health benefits, consistent with national physical activity guidelines. However, when it comes to advising patients on exercise to reduce fracture risk, guidelines should emphasize the types of exercise that have a favorable ratio of benefits relative to harms. Impact or "weight-bearing" exercises are often advised to maintain or increase bone mineral density. We define impact exercise as activities that involve peak ground reaction forces greater than or equal to 1 x body weight (e.g., running, jumping), except for walking, which is addressed in a separate question. There are no comprehensive reviews of the certainty of evidence for the effects of impact exercise on quality of life and health related outcomes, or the potential risks, in people at risk of fractures.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We performed a systematic review of studies that included impact exercises alone or combined with other interventions. The number of studies varied by outcome. We also searched for systematic reviews of impact exercise in older adults. **Desirable effects:** **Mortality:** There were no studies that examined effects on mortality in our population, so we used indirect evidence from an observational study in older adults. There is very low certainty evidence that impact exercise can reduce premature mortality (RR 0.66, 95% CI 0.53 to 0.81). **Falls, Fractures and Bone Mineral Density (BMD):** There was not enough evidence to make conclusive statements about effects on falls or fractures. Impact exercise may have a small positive effect on femoral neck BMD (MD 0.04 g/cm^2 higher, 95% CI 0.02 to 0.07, 174 participants, low certainty evidence). Our findings related to BMD are consistent in direction with a 2012 Cochrane meta-analysis conducted in postmenopausal women that reported impact exercise increased femoral neck BMD (mean % difference 1.55; 95% CI 1.41 to 1.69, four studies and 179 participants). **Physical functioning:** There is very low certainty evidence that impact exercise may improve physical functioning. Twelve studies measured physical functioning using a variety of tests. Outcomes were pooled based on the following categories: 1) *overall mobility*, using the TUG, the time to walk 20-meters, the 8-Foot Up and Go Test, and the stair climbing test; 2) *gait speed*, assessed with the 10-meter walk test and walking speed; 3) *walking distance*, assessed with the 6-minute walk test and the distance walked in 2 minutes; and 4) *lower limb strength*, measured with the 2 or 3-minute step test and the 30-second sit-to-stand test. Pooled results suggest impact exercises alone or as part of a multicomponent intervention improved TUG scores by 0.77 seconds (95% CI -0.90 to -0.65, I2 93%, 5 studies, 366 participants) and sensitivity analysis of impact only trials were similar (MD -0.95, 95% -1.09 to -0.81, 255 participants, 2 studies, low certainty). Impact exercises alone or as part of a resistance training program improved overall mobility (SMD - 0.69, 95% CI -0.88 to -0.50, I2 95%, 507 participants, 6 studies), walking speed (SMD 0.72, 95% CI 0.51 to 0.93, I2 69%, 380 participants, 5 studies, low certainty) and walking distance (SMD 1.14, 95% CI 0.82 to 1.45, 182 participants, 2 studies). Sensitivity analyses suggest impact exercise alone also increased walking speed (SMD 0.71, 95% CI 0.49 to 0.93, I2 77%, 355 participants, 4 studies) and lower limb strength (SMD 1.29, 95% CI 0.95 to 1.64, 166 participants, 3 studies). Lastly, after 12 months, Bolton 2012 reported improvements in the Time Loaded Standing Test in the multicomponent exercise group (mean 181, SD 71, 19 participants) compared to the control (mean 147, SD 77, 18 participants). **Quality of Life:** Ten studies measured health-related quality of life using generic questionnaires or disease-specific tools. Pooled results suggest that low and high impact exercises did not improve QUALEFFO-41 scores (MD 0.06, 95% CI -2.18 to 2.30, I2 54%, 265 participants, 4 studies, moderate certainty). When the Bergland 2011 trial was removed, which was the only study to enroll participants with vertebral fractures, QUALEFFO-41 scores were still not statistically significant, but the heterogeneity was reduced (MD 2.93, 95% CI -0.40 to 6.26, I2 0%, 170 participants, 3 studies). We pooled six studies using generic and disease specific tools and found impact exercise alone or as part of a multicomponent intervention improved health-related quality of life (SMD 0.37, 95% CI 0.20 to 0.55, I2 24%, 774 participants, 6 studies) and sensitivity analysis of impact only trials suggest similar results (SMD 0.37, 95% CI 0.19 to 0.55, I2 80%, 757 participants, 5 studies, moderate certainty evidence). Four studies were not pooled because a total score was not reported. These four studies suggest impact exercise alone or as part of a resistance training program may improve certain domains associated with health-related quality of life such as mental health, emotion, physical function, symptoms, leisure/social activity, and general self-assessment. **Note:** Combined interventions (e.g., impact combined with resistance training) are common, and there are few trials that study impact exercise exclusively, making it difficult to discern the independent effects of impact exercise. For example, Watson et al (2017) used high impact combined with progressive resistance training and reported significant improvements in spine and hip BMD and physical performance.	There was considerable variability in the type of impact interventions. Many used stepping exercises and agility training, whereas only one used high impact training. Therefore, the type or magnitude of impact may modify the effect and should be explored further. The results may not be generalizable to all people with osteoporosis, since people who participate in studies appear to have good physical functioning or quality of life at baseline and may be at lower risk of fractures. There was not enough data to do a subgroup analysis for people with vertebral fractures.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with impact exercises
Health	265	⨁⨁⨁◯	-	The mean	MD **0.06**

Related Quality of Life assessed with: QUALEFFO-41 (score presented as higher score is better) Scale from: 0 to 100 follow up: mean 4 months	(4 RCTs)	MODERATE[a]		health Related Quality of Life ranged from **20-31** points	**points lower** (2.18 lower to 2.3 higher)
Physical functioning assessed with: Timed Up and Go, lower score is better Scale from: 7 to 30 follow up: mean 5 months	255 (2 RCTs)	⨁⨁◯◯ LOW[b,c]	-	The mean physical functioning was **12** seconds	MD **0.95 seconds lower** (1.09 lower to 0.81 lower)
Number of Falls follow up: mean 7.5 months	294 (3 RCTs)	⨁⨁◯◯ LOW[a,b,d]	-	There do not appear to be differences in fall rates, however trials were underpowered and not pooled.	
Femoral neck BMD (surrogate for hip fracture) Scale from: 0.75g/cm^2 to 0.95g/cm^2 follow up: range 8 months to 13 months	136 (2 RCTs)	⨁⨁◯◯ LOW[e,f,g]	-	The mean femoral neck BMD (surrogate for hip fracture) ranged from **0.68-0.74** g/cm^2	MD **0.04 g/cm^2 higher** (0.02 higher to 0.07 higher)
Fragility Fractures follow up: mean 9.5 months	302 (3 RCTs)	⨁⨁◯◯ LOW[d,h]	-	Chao (2005) reported no fragility fractures in the low-to-moderate impact (n=44) and control group (n=30) while Smulders (2010), one fracture in the low impact group (n=45) and three in the control (n=47). Korpelainen (2006) noted six fractures in moderate-to-high impact group (n=67) and 15 in the control (n=69).	
All-Cause Mortality follow up: mean 11 years	1000 (1 observational study)	⨁◯◯◯ VERY LOW[i,j]	**RR 0.66** (0.53 to 0.81)	Study population	
				78 per 1,000	**27 fewer per 1,000** (37 fewer

						to 15 fewer)

a. Confidence interval crosses the clinical decision threshold
b. Effect size is overestimated or underestimated by studies that did not perform an "intention-to-treat-analysis"
c. Unexplained heterogeneity between studies
d. Wide variance of point estimates across studies
e. Note: Bone Mineral Density of the "Total Hip" had similar results (MD 0.07g/cm^2 higher, 95% CI 0.03- 0.1), but the overall certainty of the evidence was low
f. Mean and standard deviations were estimated using a WebPlotDigitizer
g. Small sample size (n<150)
h. The event rate is low but the sample size is not large (<< 2000)
i. Population is indirect (Brazilian older adults 60 years and older and it is unclear if they have osteoporosis)
j. High bias: coders not blinded to risk factors or predictor variables and there is missing data on survival rates

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
● Don't know

RESEARCH EVIDENCE

We performed a systematic review of studies that included impact exercises alone or combined with other interventions. The number of studies varied by outcome. We also searched for systematic reviews of impact exercise in older adults.

Undesirable effects: Studies did not mention serious adverse events. Some people in impact exercise studies report musculoskeletal pain during or after the intervention. However, adverse events are often assessed only in intervention groups. We do not know whether control group participants also experience pain. The undesirable effects are trivial or unknown. A subgroup analysis from one trial (Watson et al, 2019) reported no new vertebral or other fractures in individuals who performed high impact and high intensity resistance training. However, the sample included only half of the participants from the original trial, thus the sample size is relatively low.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with impact exercises
Serious Adverse Events - not reported	-	-	-	-	-
Minor Adverse Events follow up: mean 10 months	165 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b,c,d]	-	Musculoskeletal pain may occur. It is often measured in intervention group only so hard to determine between group differences.	

a. Effect size is overestimated or underestimated by studies

ADDITIONAL CONSIDERATIONS

Adverse events are poorly reported and there is differential adjudication between intervention and control, making it difficult to ascertain harms.

	that did not perform an "intention-to-treat-analysis" b. Unblinded outcome assessors c. Lack of allocation concealment d. Wide variance of point estimates across studies	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	For quality of life, there is moderate certainty of a small benefit. For other outcomes, such as fractures, physical functioning and disability and adverse events, the certainty of the evidence of effects is low or very low.	

Outcomes	Importance	Certainty of the evidence (GRADE)
Health Related Quality of Life assessed with: QUALEFFO-41 (score presented as higher score is better) Scale from: 0 to 100 follow up: mean 4 months	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Physical functioning assessed with: Timed Up and Go, lower score is better Scale from: 7 to 30 follow up: mean 5 months	CRITICAL	⨁⨁◯◯ LOW[b,c]
Number of Falls follow up: mean 7.5 months	CRITICAL	⨁⨁◯◯ LOW[a,b,d]
Femoral neck BMD (surrogate for hip fracture) Scale from: 0.75g/cm^2 to 0.95g/cm^2 follow up: range 8 months to 13 months	CRITICAL	⨁⨁◯◯ LOW[e,f,g]
Fragility Fractures follow up: mean 9.5 months	CRITICAL	⨁⨁◯◯ LOW[d,h]
Serious Adverse Events - not reported	CRITICAL	-
Minor Adverse Events follow up: mean 10 months	IMPORTANT	⨁◯◯◯ VERY LOW[b,d,i,j]
All-Cause Mortality follow up: mean 11 years	CRITICAL	⨁◯◯◯ VERY LOW[k,l]

a. Confidence interval crosses the clinical decision threshold
b. Effect size is overestimated or underestimated by studies that did not perform an "intention-to-treat-analysis"
c. Unexplained heterogeneity between studies
d. Wide variance of point estimates across studies
e. Note: Bone Mineral Density of the "Total Hip" had similar results (MD 0.07g/cm^2 higher, 95% CI 0.03- 0.1), but the overall certainty of the evidence was low

	f. Mean and standard deviations were estimated using a WebPlotDigitizer g. Small sample size (n<150) h. The event rate is low but the sample size is not large (<< 2000) i. Unblinded outcome assessors j. Lack of allocation concealment k. Population is indirect (Brazilian older adults 60 years and older and it is unclear if they have osteoporosis) l. High bias: coders not blinded to risk factors or predictor variables and there is missing data on survival rates	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The following outcomes were selected as a priority by >75% of respondents to a survey of 1108 members of the Canadian Osteoporosis Patient Network (96% were women; 86% were people living with OP, and the remaining 14% included caregivers and fitness instructors): Preserving quality of life and well-being. Preventing fracture related death Preventing admission to long-term care Preserving ability to perform daily activities Preventing all fractures related to osteoporosis Avoiding serious side-effects from drugs A survey in exercise professionals revealed similar priorities. Our working group of researchers, clinicians and a patient advocate used this information to identify the following outcomes as critical when making decisions about exercise: - mortality and fracture-related mortality - hip fractures and other fragility fractures - function and disability - quality of life - fall related injuries (or falls) - the potential for serious harm Non-serious adverse events were identified as important, but not critical outcomes. Bone mineral density was considered an indirect outcome related to hip or other fragility fractures when data on fractures were not available, but it was not a critical or important outcome on its own.	Patients place the highest value on physical functioning, quality of life, and preventing fractures and fracture-related disability or mortality. We believe we have captured the main outcomes that people value. However, different patients may value the desirable and undesirable effects differently, and their values may change over time, or as their circumstances change. Most patients would likely place a high value on a potential reduction in fall or fracture risk and related disability or mortality, or improvement in quality of life or physical functioning, and accept a potential small increase in risk of minor adverse events. Some people may overlook a lack of information on harms if there is a small potential for benefit. There may be a proportion of patients who might not be willing or able to accept potential risks e.g., low physical capacity, social/emotional barriers, high fall or fracture risk. People who are fearful of fractures, falls or adverse events may be concerned if information about risks is uncertain.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The potential for benefit outweighs what we know of the potential harms.	There is variability in the potential benefits, and the potential for adverse events is not well known.

Equity

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Initiation of some types of impact exercise may require formal instruction, particularly in someone at high risk of fracture. Therefore, there may be a cost, or concerns with access which could create health inequity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Four high quality studies were used to estimate adherence to impact exercise; in general, adherence was acceptable. Liu-Ambrose et al (2004) reported a mean adherence rate of 87%. to agility training that included dance movements, ball games and an obstacle course (supervised group exercise). Bergland et al (2011) reported that 24.4% of women attended less than 19 sessions of an agility training intervention (supervised). Watson et al (2018) reported a mean adherence rate of 92% (SD 11%) for a multimodal intervention that involved strength training and jumping chin ups with drop landings (supervised group exercise). Sherrington et al (1997) reported that adherence ranged from 60 to 100% to a stepping intervention (unsupervised home exercise). Barriers to exercise include (Ziebart et al, 2018): - fear of injury - things that influence physical capability (e.g., pain, comorbid conditions) - lack of knowledge regarding how to perform exercise safely and effectively - cost of and access to instruction, transportation - instructors without expertise in osteoporosis - programs that lack sufficient challenge or progression - variable preferences and needs based on gender or life roles	Supervised interventions may have better adherence. Higher impact exercise may be difficult to tailor and progress safely without instruction. The time commitment required to participate in structured programs may be a barrier, especially if people are working or have other demands on their time. Individuals with pelvic floor dysfunction may have concerns about performing impact exercise. They may require additional exercises to strengthen the pelvic floor muscles.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no studies on the feasibility of implementing impact exercise, although there are studies that have implemented it in a research setting. Cost may influence feasibility. There are no studies specific to the resource requirements or savings associated with impact exercise alone, or in people with low bone mass. Patil et al (2011) conducted a two-year RCT in Finland evaluating a multimodal exercise program in women aged 70-80 years living independently, where the exercise included supervised progressive strength training, impact exercise, and balance and agility training delivered in a group setting (~1 instructor for 10 participants). They reported a 93% probability that the cost to avoid an injurious fall via participation in exercise was €708 ($1037 Canadian dollars) per person per year. They estimated that there was an 85.6 % chance of the exercise intervention being cost-effective in this population at a willingness to pay €3000 ($4393 Canadian) per injurious fall prevented.	Impact exercises can be performed with little or no equipment, and so could be done with zero cost. Patients may wish to have guidance on how to start safely, and how to progress their exercises (e.g., $335 for assessment and five sessions with an exercise physiologist). The costs can be lower if one chooses exercise in a group (e.g., small group personal training, strength-based group classes included in membership) or attends subsidized or free community-based classes or other services (e.g., cardiac rehabilitation, YMCA programs for people with chronic conditions). However, not all programs include progressive impact exercise, and the adherence to, and benefits and harms may vary with environment, level of instruction and qualifications of instructor. It may be necessary to ensure that any program or instructor are delivering impact exercise at a comparable dose and intensity as in studies that demonstrated benefits. It is ideal if exercises are tailored to the person based on an assessment of individual capabilities. We need to balance safe initiation and progression of impact exercise in people at risk of fractures, and not being so restrictive that we create activity avoidance. Access to

		instruction and fear of doing impact exercise may be barriers to feasibility, and thus it may not be perceived as feasible for all people.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Individuals who want to participate in other activities (e.g., impact exercise) for enjoyment or other benefits should be encouraged to do them, if they can be done safely or modified for safety (GRADE: conditional recommendation, very low certainty evidence). Other activities should be encouraged in addition to, but not instead of, balance, functional, and resistance training.

Remark: Encourage a variety of types and intensities of physical activity in accordance with the Canadian 24-Hour Movement Guidelines (https://csepguidelines.ca), such as getting ≥ 150 minutes of moderate to vigorous physical activity, but prioritize balance, functional, and resistance training. If participating in impact exercise, only progress to moderate (e.g., running, racquet sports, skipping) or high (e.g., drop or high vertical jumps) impact exercise if appropriate for fracture risk or physical fitness level; safety or efficacy is uncertain in individuals at high fracture risk (e.g., history of spine fracture or 10-year fracture risk for major osteoporotic fracture of ≥20% calculated by FRAX or Canadian Association of Radiologists and Osteoporosis Canada tools).

Good practice statement: Activities that involve rapid, repetitive, sustained, weighted, or end range of motion twisting or flexion of the spine may need to be modified, especially in individuals at high risk of fracture. When available, seek advice from exercise professionals who have training on osteoporosis for exercise selection, intensity and progression, and activity modification, especially after recent fracture or if at high risk of fracture. When not available, refer to Osteoporosis Canada resources.

Justification

Impact exercise may improve physical functioning and BMD, and reduce mortality, but the evidence overall is of very low certainty. There is very little evidence in individuals at high risk of fracture. Many studies used multimodal interventions that combined impact exercise with other types of exercise, such as resistance training or balance training. Thus, the certainty of evidence and size of effect was insufficient to support a separate recommendation for impact exercise for all people. Impact exercise and progressive resistance training are the only types of exercise that may have a small effect on bone mineral density, so some individuals may be interested in pursuing impact exercise to maintain or improve bone mineral density. All individuals can start with low impact exercise, progressing to moderate (e.g., aerobics) or high (e.g., jumping) impact if appropriate for fracture risk or physical fitness level. Impact exercise may need to be combined with strength training to observe effects on BMD and ensure that muscles are properly conditioned for this type of exercise.

Subgroup considerations

We considered subgroup analysis of studies of impact exercise in people with a history of vertebral fractures, but there was insufficient evidence to do so.

Implementation considerations

Impact exercise can be recommended alongside other interventions with stronger evidence for benefit relative to harm, such as functional and balance training and resistance training. We need to balance safe initiation and progression of impact exercise in people at risk of fractures, and not being so restrictive that we create activity avoidance. When initiating or progressing to higher impact exercise, a qualified exercise professional should be consulted, particularly for individuals at high risk of fracture, or with a history of vertebral or hip fracture(s). Individuals with pelvic floor dysfunction may have concerns about performing impact exercise. They may require additional exercises to strengthen the pelvic floor muscles, and may need to perform low or moderate impact exercise only. All exercise programs should consider appropriate warm-up and cool-down activities, and consideration of breathing, alignment and safety precautions.

Monitoring and evaluation

It would be useful to monitor:
- understanding and acceptability of different types of impact exercise, and barriers to and facilitators of impact exercise among individuals at risk of fracture
- the harms of impact exercise
- participation in impact exercise at the population level, and in individuals at risk of fractures

Research priorities

Future research should consider:
- whether impact exercise alone has an effect on outcomes important to patients, or only when combined with resistance training or other types of exercise
- whether high impact is needed, or if moderate impact is sufficient for improving outcomes important to patients
- the harms of impact exercise, particularly among individuals at high risk of fractures.

Researchers should improve the quality of adverse event reporting (including monitoring adverse events in all study arms) in exercise trials. Where possible, observational studies or clinical trials assessing whether impact exercise results in clinical or morphometric vertebral fractures would be useful in informing future guidelines

QUESTION 2: SHOULD WALKING VS. NO INTERVENTION BE USED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER AT INCREASED RISK OF FRACTURE?

Should walking vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?	
POPULATION:	Postmenopausal females and males aged 50 years and older at increased risk of fracture
INTERVENTION:	walking
COMPARISON:	no intervention
MAIN OUTCOMES:	Health-related Quality of Life; Physical functioning; Number of Falls; Fall-Related Fractures; Femoral Neck BMD (surrogate for hip fractures); Lumbar Spine BMD (surrogate for fragility fractures); Serious Adverse Events; All-Cause Mortality;
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	We are updating the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada (section on exercise) as well as the Too Fit to Fracture Recommendations.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low bone strength can increase the risk of bone fractures. One in three women and one in five men over the age of 50 will experience a fracture due to low bone strength. Fractures can cause pain or impaired mobility. People who have hip or vertebral fractures are more likely to die prematurely, often because of fracture-related complications. Exercise is often recommended to reduce fracture risk, but there are many types of exercise. Some types of exercise may have more benefits when it comes to health or quality of life than others. Moreover, patients and health care providers may be concerned about the potential for harms with some types of exercise. Patients should be encouraged to perform regular physical activities that they enjoy for overall health benefits, consistent with national physical activity guidelines. However, when it comes to advising patients on exercise as a way to reduce fracture risk, guidelines should emphasize the types of exercise that have a favorable ratio of benefits relative to harms. Walking is considered a weight-bearing exercise that is safe, generalizable to most people, and requires minimal supervision or equipment. Walking has been associated with many health benefits in the general population e.g., positive effects on mental health, body mass, body mass index, body fat, systolic and diastolic blood pressure, fasting glucose and cardiovascular fitness (Oja et al, 2018). To inform guidelines for the management of osteoporosis and for fracture prevention, we reviewed the benefits (e.g., effects on falls, fractures, physical functioning, quality of life) and harms of walking in people at risk of fractures.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large	We performed a systematic review of walking interventions in people who are at risk of fracture, often defined based on low bone mineral density. We also performed a search for systematic reviews of walking in older adults. **Desirable Effects**	For many outcomes there is only one study looking at walking in people with low bone mass, so the potential benefits are uncertain. The uncertainty regarding the

○ Varies ○ Don't know	**Fractures and BMD:** Our systematic review revealed that there are few RCTs of walking interventions in individuals at risk of fracture (Rodrigues et al, 2021). Pooled estimates from two RCTs suggest that walking may improve mobility or quality of life, but effects are uncertain. One RCT reported 2 fractures in the exercise group and 3 in the control group (n=97). A 2019 Cochrane review in older adults reported data from one trial that effects of walking on fall-related fractures are uncertain (RR 0.66, 95%CI 0.11 to 3.76; 97 participants, very low-certainty evidence). There is very low certainty evidence that walking may increase BMD. Similarly, a 2012 Cochrane review reported no effect of lower impact activities (e.g., walking, Tai Chi) on hip BMD in postmenopausal women, but a modest effect on spine BMD (Howe et al, 2011). **Falls:** We found one RCT that provides very low certainty evidence that walking may increase the risk of falls in people at risk of fracture, findings that are consistent with the most recent Cochrane review of exercise for fall prevention in older adults, which suggests uncertain effects of walking on rate of falls (RaR 1.14, 95% CI 0.66 to 1.97; 441 participants, 2 studies; very low-certainty evidence) or risk of being a person who falls (RR 1.05, 95% CI 0.71 to 1.54; 441 participants, 2 studies; very low certainty evidence). **Mortality:** While observational research suggests that walking can reduce mortality risk by 11% (95% CI = 4 to 17%), studies like these are often not specific to older adults or people with osteoporosis, so present very indirect evidence (Kelly et al, 2014). **Physical Functioning:** There is very low certainty evidence that walking can improve physical functioning. Nordic walking alone or walking as part of a multicomponent intervention may improve the distance walked over 6 min (MD 39.37 m, 95% CI [21.83, 56.91], I2 = 45% 400 participants, three studies, very low certainty); heterogeneity disappears when the Nordic walking study is removed. Pooled results from two quasi-RCTs indicate Nordic walking may improve TUG scores by 1.39 s (95% CI [1.00, 1.78], I2 =100%, 86 participants, very low certainty). Other studies reported improvements in repeated chair stand tests and timed loading standing, but others reported no effect on gait speed. **Quality of Life:** There do not appear to be significant effects of walking on quality of life, but the evidence is of very low certainty.	potential benefits is consistent with studies that combine walking and other interventions, and with a meta-analysis of the effects of walking on falls and fractures. Adverse events are not reported, and there is potential for an increase in falls. The adherence to, and benefits and harms of walking may vary with intensity or environment as well as individual factors that influence falls risk. Walking may have other health benefits. e.g., effects on mental health, body mass, body mass index, body fat, systolic and diastolic blood pressure, fasting glucose and cardiovascular fitness (Oja et al, 2018).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with walking
Health-related Quality of Life assessed with: QUALEFFO-41 (score presented so that higher score is better) Scale from: 0 to 100 follow up: range 5 weeks to 12 weeks	211 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean health-related Quality of Life was **38.1** points	MD **1.25 points higher** (0.28 lower to 2.77 higher)
Physical functioning assessed with: Timed Up and Go	86 (2 RCTs)	⨁◯◯◯ VERY LOW[c,d,e,f]	-	The mean physical functioning ranged from **25-35** seconds	MD **1.39 seconds lower** (1.78 lower to 1 lower)

follow up: mean 12 months					
Number of Falls follow up: mean 6.5 months	102 (1 RCT)	⨁◯◯◯ VERY LOW[b,c,g]	**RR 1.55** (1.15 to 2.09)	Study population	
				52 per 100	**29 more per 100** (8 more to 57 more)
Fall-Related Fractures follow up: 12 months	97 (1 RCT)	⨁⨁◯◯ LOW[b,c]	**RR 0.66** (0.11 to 3.76)	Study population	
				6 per 100	**2 fewer per 100** (6 fewer to 17 more)
Femoral Neck BMD (surrogate for hip fractures) follow up: mean 12 months	97 (1 RCT)	⨁⨁◯◯ LOW[c,g]	-	The mean femoral Neck BMD (surrogate for hip fractures) ranged from **0.68 - 0.74** g/cm^2	MD **0.01 g/cm^2 lower** (0 to 0.03 lower)
Lumbar Spine BMD (surrogate for fragility fractures) follow up: mean 12 months	139 (1 RCT)	⨁⨁◯◯ LOW[c,g]	-	The mean lumbar Spine BMD (surrogate for fragility fractures) ranged from **0.920 to 1.021** g/cm^2	MD **0.01 g/cm^2 higher** (0 to 0.03 higher)
All-Cause Mortality follow up: median 7 years	1000 (5 observational studies)	⨁◯◯◯ VERY LOW[f,h,i]	**RR 0.89** (0.82 to 0.96)	Study population	
				78 per 1,000	**9 fewer per 1,000** (14 fewer to 3 fewer)

a. Studies include walking as part of a multicomponent exercise combined with either impact or resistance training
b. Wide confidence intervals
c. Small sample size (N < 100)
d. Effect size may be overestimated or underestimated by lack of "intention-to-treat" analysis
e. Selective outcome reporting
f. Unexplained heterogeneity between studies
g. Other sources of bias: results are difficult to interpret
h. Does not include the population of interest
i. Kelly 2014: Random effects meta-analysis of point estimates from 18 results from 14 walking studies. Corresponding walking exposure was equivalent to 11.25 MET.hours per week.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	We performed a systematic review of walking interventions in people who are at risk of fracture, often defined based on low bone mineral density. We also performed a search for systematic reviews of walking in older adults. **Harms** Twelve of the 13 studies did not discuss adverse events; Smulders et al. (2010) reported no adverse events during their study.	People may need to find an indoor place to walk in inclement weather.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with walking
Serious Adverse Events follow up: mean 12 months	109 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	-	Adverse events did not appear to be different between groups with different levels of adherence to walking.	

a. Effect size may be overestimated or underestimated by lack of "intention-to-treat" analysis
b. Wide confidence intervals

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	For many critical outcomes, the quality of evidence is very low.	

Outcomes	Importance	Certainty of the evidence (GRADE)
Health-related Quality of Life assessed with: QUALEFFO-41 (score presented so that higher score is better) Scale from: 0 to 100 follow up: range 5 weeks to 12 weeks	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Physical functioning assessed with: Timed Up and Go follow up: mean 12 months	CRITICAL	⨁◯◯◯ VERY LOW[c,d,e,f]
Number of Falls follow up: mean 6.5 months	CRITICAL	⨁◯◯◯ VERY LOW[b,c,g]

Fall-Related Fractures follow up: 12 months	CRITICAL	⨁⨁◯◯ LOW[b,c]
Femoral Neck BMD (surrogate for hip fractures) follow up: mean 12 months	CRITICAL	⨁⨁◯◯ LOW[c,g]
Lumbar Spine BMD (surrogate for fragility fractures) follow up: mean 12 months	CRITICAL	⨁⨁◯◯ LOW[c,g]
Serious Adverse Events follow up: mean 12 months	CRITICAL	⨁◯◯◯ VERY LOW[b,d]
All-Cause Mortality follow up: median 7 years	CRITICAL	⨁◯◯◯ VERY LOW[f,h,i]

a. Studies include walking as part of a multicomponent exercise combined with either impact or resistance training
b. Wide confidence intervals
c. Small sample size (N < 100)
d. Effect size may be overestimated or underestimated by lack of "intention-to-treat" analysis
e. Selective outcome reporting
f. Unexplained heterogeneity between studies
g. Other sources of bias: results are difficult to interpret
h. Does not include the population of interest
i. Kelly 2014: Random effects meta-analysis of point estimates from 18 results from 14 walking studies. Corresponding walking exposure was equivalent to 11.25 MET.hours per week.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The following outcomes were selected as a priority by >75% of respondents to a survey of 1108 members of the Canadian Osteoporosis Patient Network (96% were women; 86% were people living with OP, and the remaining 14% included caregivers and fitness instructors): Preserving quality of life and well-being. Preventing fracture related death Preventing admission to long-term care Preserving ability to perform daily activities Preventing all fractures related to osteoporosis Avoiding serious side-effects from drugs A survey in exercise professionals revealed similar priorities. Our working group of researchers, clinicians and a patient advocate used this information to identify the following outcomes as critical when making decisions about exercise: - mortality and fracture-related mortality - hip fractures and other fragility fractures - function and disability - quality of life - fall related injuries (or falls) - the potential for serious harm Non-serious adverse events were identified as important, but not critical outcomes. Bone mineral density was considered an indirect outcome related to hip or other	Some people may value the other potential benefits of walking, outside of those that we have considered. Patients place the highest value on physical functioning, quality of life, and preventing fractures and fracture-related disability or mortality. We believe we have captured the main outcomes that people value. However, patients may value the desirable and undesirable effects differently, and their values may change over time, or as their circumstances change. Most patients would likely place a high value on a potential reduction in fall or fracture risk and related disability or mortality, or improvement in quality of life or physical functioning, and accept a potential small increase in risk of minor adverse events. Some people may overlook a lack of information on harms if there is a small potential for benefit. There may be a proportion of patients who might not be

	fragility fractures when data on fractures were not available, but it was not a critical or important outcome on its own.	willing or able to accept potential risks e.g., low physical capacity, social/emotional barriers, high fall or fracture risk. People who are fearful of fractures, falls or adverse events may be concerned if information about risks is uncertain.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	For many outcomes, the desirable effects are uncertain. There is some indirect evidence that walking may reduce mortality. The undesirable effects of walking are uncertain.	Walking may have other health benefits. e.g., mental health, effects on body mass, body mass index, body fat, systolic and diastolic blood pressure, fasting glucose and cardiovascular fitness (Oja et al, 2018). The balance between benefits and harms may depend on whether patients value the other benefits. The adherence to, and benefits and harms of walking may vary with intensity (e.g., brisk vs leisurely walking) or environment, as well as individual factors that influence falls risk.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know		Walking as a physical activity option may increase equity because it is feasible to implement without major costs.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Only one low quality trial that was exclusively walking reported a mean adherence rate of 84.4%. Adherence in multimodal interventions ranged from 39% to 100%.	Walking is not intimidating to learn or try. Walking may be seen as desirable because of other benefits, preference, or convenience (e.g., effects on mental health, blood pressure, body mass, walking with friends or pets). Weather conditions (e.g., snow, ice, rain) may influence adherence or seasonal acceptability. While walking may be perceived as more acceptable, adherence to walking programs may not be better than for other types of exercise.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are no studies exploring the feasibility of walking in people with low bone mass. Few exercise studies exclusively study walking in this population. A study examining the feasibility of an interactive workshop to promote outdoor walking alone or combined with a walking group in older adults with low physical activity levels reported low recruitment rates and average adherence of <61%, with the following barriers noted: motivation, and fear of injury, falls, or pain, and the potential for an increased risk of injury when walking outside, particularly in the	Implementing walking would be feasible, because it is not costly, it is accessible, and requires no equipment. Walking may be difficult to implement in winter or adverse weather conditions, especially for people who are fearful of falls or fractures. It may be necessary to ensure that walking

	winter (Barclay et al 2018). There are no major costs of walking, unless weather or other reasons dictate that one must drive somewhere to walk indoors. However, intervention studies that use walking often include some instruction to ensure sufficient intensity, and to support behaviour change to achieve adequate adherence. The Lifestyle Interventions and Independence for Elders (LIFE) physical activity intervention involved twice weekly workshops to promote increased participation in walking and other physical activities. It demonstrated a reduction in incident mobility disability in at risk older adults (HR=0.82, 95%CI=0.69–0.98, p=0.03)), and cost $3302 per participant (e.g., exercise professionals, staff time to do reminder calls, pedometers, snacks and materials, incentives). Groessl et al (2016) reported that for the LIFE exercise intervention, the incremental cost-effectiveness ratios were US$42,376/major mobility disability prevented and US$49,167/QALY. A primary care-based physical activity counselling intervention (i.e., endorsement by physician plus 4 sessions by health counselor) targeting increased physical activity level and gait speed cost $696 per participant to deliver (Cowper et al, 2017).	programs are performed at a comparable dose and intensity as in studies that demonstrated benefits, using similar strategies to ensure adequate adherence.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Individuals who want to participate in other activities (e.g., walking, Nordic walking) for enjoyment or other benefits should be encouraged to do them, if they can be done safely or modified for safety (GRADE: conditional recommendation, very low certainty evidence). Other activities should be encouraged in addition to, but not instead of, balance, functional, and resistance training.
Remark: Encourage a variety of types and intensities of physical activity in accordance with the Canadian 24-Hour Movement Guidelines (https://csepguidelines.ca), such as getting ≥ 150 minutes of moderate to vigorous physical activity, but prioritize balance, functional, and resistance training.

Justification

Observational studies suggest that walking may reduce mortality in adults (very low certainty evidence). Effects on fractures, falls, quality of life and physical functioning, or potential harms in people at risk of fractures are unknown (very low certainty evidence). Walking is low cost, feasible and acceptable. Canadian 24-Hour Movement Guidelines recommend getting 150 minutes per week or more of moderate-vigorous physical activity for overall health benefits, resistance training twice weekly, and reducing sedentary time, as well as balance exercise for older adults.

Subgroup considerations

We planned to perform a subgroup analysis related to Nordic walking, but the available evidence was of very high risk of bias and did not meet our criteria for inclusion. Therefore, the benefits relative to the harms of Nordic walking are uncertain. Our recommendations are neither for nor against Nordic walking; if patients prefer Nordic walking to regular walking, they can choose to do it as a means to meet national physical activity guidelines for the general population, as long as it is not recommended to the exclusion of other interventions where there is stronger evidence of benefit relative to harm. We planned to perform a subgroup analysis in individuals with vertebral fractures. There was insufficient evidence to do so.

Implementation considerations

Any knowledge translation pertaining to exercise for osteoporosis should only emphasize brisk walking as an intervention if coupled with other interventions where there is stronger evidence for benefits relative to harms, such as functional strength and balance training, or resistance training. Walking may be more difficult to implement outdoors in winter or adverse weather conditions, especially for people who are fearful of falls or fractures. Proper footwear or assistive aids, and avoidance of trip hazards should be considered where needed. To achieve health benefits, walking should be brisk, or performed at moderate or vigorous intensity. It may be necessary to ensure that walking programs are performed at a comparable dose and intensity as in studies that demonstrated benefits, using similar strategies to ensure adequate adherence. All exercise programs should consider appropriate warm-up and cool-down activities, and consideration of safety precautions. Individuals with impairments, activity limitations or participation restrictions that make it difficult to adhere to the guidelines may need advice from a health care professional or exercise professional on how to adapt the guidelines.

Monitoring and evaluation

It would be useful to monitor:
-how acceptable a "conditional recommendation for" walking is to patients and health care providers, given its ubiquity in public health messaging;
-how often recommendations to patients include walking, with or without other types of exercise;
-how often fractures or falls occur as a result of walking for exercise, leisure, daily activities or transportation.

Research priorities

It may be difficult to justify or implement RCTs of walking in people at risk of fracture. Nordic walking poles act as a support object and may be perceived as safer, and also more challenging for arm and core muscles; whether there are clinically meaningful benefits or reduced harms would need to be verified in future research. If evidence pertaining to Nordic walking is identified as a research priority among patients or other stakeholders, we suggest comparing walking to an active attention control. We suggest that researchers conducting future observational studies with fall or fracture outcomes consider better ascertainment of harms, and implementing objective measures of physical activity combined with physical activity logs or questionnaires so that we can study whether different intensities of physical activity are associated with fracture risk or falls and begin to identify the types of physical activity that are associated with benefit or harm.

QUESTION 3: SHOULD PROGRESSIVE RESISTANCE TRAINING VS. NO INTERVENTION BE USED POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER AT INCREASED RISK OF FRACTURE?

Should progressive resistance training vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?	
POPULATION:	Postmenopausal females and males aged 50 years and older at increased risk of fracture
INTERVENTION:	progressive resistance training
COMPARISON:	no intervention
MAIN OUTCOMES:	Quality of Life; Physical functioning; Number of Fallers; Fall-related injuries; Femoral neck BMD (surrogate for hip fractures); Fragility Fractures; Mortality; Serious Adverse Events; Minor Adverse Events;
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	We are updating the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada (section on exercise) as well as the Too Fit to Fracture Recommendations.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low bone strength can increase the risk of bone fractures. One in three women and one in five men over the age of 50 will experience a fracture due to low bone strength. Fractures can cause pain or impaired mobility. People who have hip or vertebral fractures are more likely to die prematurely, often because of fracture-related complications. Progressive resistance training is where muscles work against resistance (e.g., lifting weights, lifting body weight when climbing stairs). A key feature of strength training is “overload” of the muscles, which means performing a version of the exercise that is challenging, and performing enough repetitions that the muscles are fatigued. Progressive resistance training can improve physical performance, and muscle pull on bones may stimulate maintenance or increases in bone mineral density (BMD). However, some health care providers or patients may be concerned about fracture risk during exercises that involve high muscle forces. Therefore, we sought to review the efficacy and safety of progressive resistance training in individuals 50 years of age or older who are at risk of fractures.	The risk of fracture is higher in individuals with a history of fracture. Individuals with a history of hip or vertebral fracture are at high risk, and treatment decisions may be different in this group.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We performed a systematic review of randomized controlled trials (RCTs) that examine the benefits of progressive resistance training in people over 50 years of age at risk of fracture; 1 to 12 RCTs were included, depending on the outcome (Ponzano et al, 2021). We also searched for systematic reviews of resistance training in older adults to supplement evidence where availability of trials in people at risk of fracture was low. **Desirable effects:** **Falls:** Effects on fall-related injuries or the number of people who fall are unknown, or there may be no effect or a slight increase in number of people who experience a fall. A Cochrane meta-analysis of the effects of resistance training on falls in older adults also concluded that the effects were uncertain for rate of falls (RaR 1.14, 95% CI 0.67 to 1.97; 327 participants, 5 studies) or being a faller (RR 0.81, 95% CI 0.57 to 1.15; 163 participants, 2 studies), classifying it as very low certainty evidence (Sherrington et al, 2019). However, there is moderate certainty evidence that combined interventions (e.g., resistance training combined with functional and	Heterogeneity in effect estimates for some outcomes may be due to exercise intensity, or the inclusion of combined interventions (e.g., resistance training combined with walking, aerobic exercise, or impact exercise). There were not enough trials to evaluate sources of heterogeneity. Effects on BMD may only occur when resistance training is progressive and moderate-high intensity resistance training, with or without moderate-high impact activities. The mean frequency of resistance training was thrice weekly, and the median was twice weekly.

	balance training) reduces the rate of falls (RaR 0.69, 95%CI 0.48 to 0.97; 1084	

participants, 8 studies) or risk of falling (RR 0.76, 95% CI 0.61 to 0.95; 1375 participants, 13 studies) among older adults. Functional training is defined as exercises aligned with functional tasks, like sit to stand, gait training or stair-climbing; many functional training exercises would also be considered progressive resistance training. Resistance training alone may not be effective for reducing falls, and *it may be necessary to combine functional resistance training with balance exercises.*

Fractures: Effects on fractures are uncertain; event rates are low, and studies are often underpowered. One study of exercise in individuals with vertebral fractures (Giangregorio et al, 2018) reported 32 fragility fractures (16 intervention, 16 control) unrelated to the intervention or control activities, and two additional non-fragility fractures (2 intervention, 1 control). Crotty et al (2019) reported that in a study of physical therapy visits over 1 month among individuals with a history of hip fracture there were three hip fractures in the intervention group (n= 119) and one hip fracture in the control group (121 participants); whether they were related to intervention was not stated. Four other studies reported 16 fractures in 363 participants after PRT alone or combined with other interventions and 32 in the control groups (271 participants), but the authors did not state whether these fractures were attributable to the interventions. An RCT in people with vertebral fractures (n=185) reported that one person experienced a fractured costal cartilage performing prone exercise, and one person experienced a fractured rib when rolling from supine to prone, and that two additional occurred during data collection (i.e., not attributable to exercise): a fractured hip diagnosed after data collection, and a fractured metatarsal from dropping a weight on a foot (Gold et al, 2004). A 2019 Cochrane review identified one study of functional strength and balance training in older adults that reported fracture data, and effects are uncertain (RR 0.97, 95% CI 0.14 to 6.49; 73 participants; very low certainty of evidence). Effects on femoral neck BMD reported in three trials are small and heterogeneous (similar findings using total hip BMD). Small positive effects on femoral neck BMD were reported in a meta-analysis of moderate-high intensity resistance training in postmenopausal women (MD +1.03 percent [95% CI 0.24, 1.82], Howe et al, 2011). However, using low weights had no effect on hip BMD.

Mortality: Among RCTs in individuals at risk of fracture, there is not enough data on mortality, as only three small RCTs reported mortality; one study reported 4 deaths in the intervention and 8 in the control group, one study reported 2 deaths in the intervention group and none in the control, and another study reported that 10 and 22 people died in the intervention and control groups, respectively. There is low certainty evidence that performing 1-2 sessions of resistance training is associated with a lower risk of death from a systematic review of cohort studies (hazard ratio 0.79, 95%CI 0.69-0.91, Saeidifard et al 2019).

Physical functioning: There is very low certainty evidence that resistance training can improve physical functioning in people at risk of fractures, measured using the Timed Up and Go test (MD 1.24 SD lower, 95% CI 1.67 lower to 0.82 lower, 241 participants, very low certainty evidence, Ponzano et al, 2021). Our findings are consistent with a 2009 Cochrane review that reported that strength training (often at high intensity) can improve measures of physical ability (33 trials, 2172 participants; SMD 0.14, 95% CI 0.05 to 0.22, Latham et al 2009). Similar effects on mobility are observed when examining studies in high-risk groups e.g., individuals with vertebral fractures (Gibbs et al, 2019). One study reported that resistance and balance training post hip fracture resulted in lower assistive device or nursing home use, but the sample size was small (Singh et al). There is moderate certainty evidence that resistance training can improve physical functioning in older adults. An overview of systematic reviews that was used to inform the Canadian 24-Hour Movement Guidelines included a systematic review by Lai et al (2018) of 21 RCTs of 875 participants that examined the effects of resistance training on muscle strength (18 studies) and physical performance (5 studies) among older adults (age range, 68–92 years). A minimum of 6 weeks of RT improved muscle strength (1RM, mean difference (MD): 12.8 kg, 95% CI: 8.5–17.0)) and physical performance (chair-stand test, MD: 2.6 more chair stands, 95% CI: 1.3– 3.9) compared with usual care. The overall risk of bias was considered "low" or "unclear" by the systematic review authors (Lai et al, 2018). The AMSTAR 2 assessment was rated as "moderate". Systematic reviews of resistance training in older adults by Raymond et al (2013) and Borde et al (2015) suggest that intensity may need to be moderate or high, and that longer training durations or time under tension of 6 seconds may be important training variables related to improving muscle strength.

Quality of life: There is moderate certainty evidence that resistance training can have a moderately sized, positive effect on quality of life (SMD 0.75 SD higher, 95% CI 0.54 higher to 0.95 higher, 412 participants).

Outcomes	№ of participants	Certainty of the evidence	Relative effect	Anticipated absolute effects* (95% CI)

	(studies) Follow up	(GRADE)	(95% CI)	Risk with no intervention	Risk difference with progressive resistance training
Quality of Life assessed with: QUALEFFO-41, SF-36, JOQoL follow up: range 1.5 months to 12 months	412 (8 RCTs)	⨁⨁⨁◯ MODERATE[a]	-	The mean quality of Life was **0** SD	SMD **0.75 SD higher** (0.54 higher to 0.95 higher)
Physical functioning assessed with: Time Up and Go test (lower is better) follow up: range 1.5 months to 12 months	886 (12 RCTs)	⨁◯◯◯ VERY LOW[a,b]	-	The mean physical functioning ranged from **7.0-16.4** SD	MD **0.89 SD lower** (1.01 lower to 0.78 lower)
Number of Fallers follow up: range 4 weeks to 12 months	631 (5 RCTs)	⨁◯◯◯ VERY LOW[a,c]	**RR 1.23** (1.00 to 1.51)	Study population	
				300 per 1,000	**69 more per 1,000** (0 fewer to 153 more)
Fall-related injuries follow up: range 4 weeks to 12 months	845 (4 RCTs)	⨁⨁◯◯ LOW[b,d]	**Rate ratio 0.65** (0.31 to 1.37)	Study population	
				53 per 1,000	**19 fewer per 1,000** (37 fewer to 20 more)
Femoral neck BMD (surrogate for hip fractures) follow up: range 8 months to 12 months	521 (5 RCTs)	⨁◯◯◯ VERY LOW[b,e,f]	-	The mean femoral neck BMD (surrogate for hip fractures) ranged from **0.728 to 0.866** g/cm^2	MD **0.02 g/cm^2 higher** (0.01 higher to 0.03 higher)
Fragility Fractures follow up: range 4 weeks to 12 months	622 (6 RCTs)	⨁⨁◯◯ LOW[b,d]	-	Effects on fragility fractures are uncertain due to a low number of events.	
Mortality follow up: range 4 weeks to 12 months	1000 (10 observational studies)	⨁⨁◯◯ LOW	**HR 0.79** (0.69 to 0.91)	Low	
				80 per 1,000	**16 fewer per 1,000** (24 fewer to 7 fewer)

a. Serious unexplained heterogeneity

b. Studies often combined resistance training with other interventions (e.g., balance, balance+impact, impact, physical therapy)
c. Confidence intervals overlap with the no difference line
d. Event rates are low and studies are underpowered.
e. Concerns with blinding, allocation concealment, randomization, intention to treat analysis in one or more studies.
f. Heterogeneity is explained by the difference of intensity across the studies

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

We performed a systematic review of randomized controlled trials (RCTs) that examine the benefits of progressive resistance training in people over 50 years of age at risk of fracture; 1 to 12 RCTs were included, depending on the outcome (Ponzano et al, 2021). We also searched for systematic reviews of resistance training in older adults to supplement evidence where availability of trials in people at risk of fracture was low. Monitoring or reporting of adverse events was inconsistent.

Undesirable effects:

There is low certainty evidence that there is no increased risk of serious adverse events (SAEs) with progressive resistance training in individuals at risk of fracture (6 studies). One study reported serious adverse events during a trial of a 12-month home PRT and balance intervention in women with vertebral fractures (Giangregorio et al 2018): eighteen events were recorded among the intervention group (n=71) versus twelve events in the control group (n=70). None was reported to be related to the intervention. Five more studies stated that no serious events related to the intervention occurred.

The effects of PRT alone or combined with other interventions on minor adverse event occurrence were uncertain (IRR 0.94, 95%CI = 0.59, 1.50, 300 participants, 4 studies, I 2 = 0%, very low-quality evidence) (Ponzano et al, 2021). There were not enough PRT only studies that could be pooled to perform a sensitivity analysis. Minor adverse events include things like muscle strain, musculoskeletal issues, or pain. An RCT in people with vertebral fractures (n=185) reported that one person experienced a fractured costal cartilage performing prone exercise, and one person experienced a fractured rib when rolling from supine to prone, and that two additional occurred during data collection (i.e., not attributable to exercise): a fractured hip diagnosed after data collection, and a fractured metatarsal from dropping a weight on a foot (Gold et al, 2004).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with progressive resistance training
Serious Adverse Events follow up: mean 12 months	501 (6 RCTs)	⨁⨁◯◯ LOW[a,b]	-	Serious adverse events attributable to resistance training were not reported. Monitoring of adverse events is not always reported.	
Minor Adverse Events follow up: range 2.5 months to 12 months	712 (5 RCTs)	⨁◯◯◯ VERY LOW[b]	**RR 0.94** (0.59 to 1.50)	Study population	
				302 per 1,000	**18 fewer per 1,000** (124 fewer to 151 more)

a. Studies often combined resistance [illegible]

ADDITIONAL CONSIDERATIONS

Heterogeneity in effect estimates for some outcomes may be due to exercise intensity, or the inclusion of combined interventions (e.g., resistance training combined with walking, aerobic exercise, or impact exercise). Effects on BMD may only occur when resistance training is progressive and moderate-high intensity resistance training, with or without moderate-high impact activities. There were few undesirable events, and some studies did not report them, or did not use systematic methods to evaluate or verify them.

interventions (e.g., balance, balance+impact, impact, physical therapy)
b. Adverse events are often reported in the intervention group only, and the number of events is low.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty of evidence was judged to be low because most critical outcomes had a certainty of low or moderate.	We place a high value on the desirable effects of resistance training on quality of life, physical functioning and bone mineral density or fracture risk.

Outcomes	Importance	Certainty of the evidence (GRADE)
Quality of Life assessed with: QUALEFFO-41, SF-36, JOQoL follow up: range 1.5 months to 12 months	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Physical functioning assessed with: Time Up and Go test (lower is better) follow up: range 1.5 months to 12 months	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Number of Fallers follow up: range 4 weeks to 12 months	CRITICAL	⨁◯◯◯ VERY LOW[a,c]
Fall-related injuries follow up: range 4 weeks to 12 months	CRITICAL	⨁⨁◯◯ LOW[b,d]
Femoral neck BMD (surrogate for hip fractures) follow up: range 8 months to 12 months	CRITICAL	⨁◯◯◯ VERY LOW[b,e,f]
Fragility Fractures follow up: range 4 weeks to 12 months	CRITICAL	⨁⨁◯◯ LOW[b,d]
Mortality follow up: range 4 weeks to 12 months	CRITICAL	⨁⨁◯◯ LOW
Serious Adverse Events follow up: mean 12 months	CRITICAL	⨁⨁◯◯ LOW[b,g]

a. Serious unexplained heterogeneity
b. Studies often combined resistance training with other interventions (e.g., balance, balance+impact, impact, physical therapy)
c. Confidence intervals overlap with the no difference line
d. Event rates are low and studies are underpowered.
e. Concerns with blinding, allocation concealment, randomization, intention to treat analysis in one or more studies.
f. Heterogeneity is explained by the difference of intensity across the studies
g. Adverse events are often reported in the intervention group only, and the number of events is low.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The following outcomes were selected as a priority by >75% of respondents to a survey of 1108 members of the Canadian Osteoporosis Patient Network (96% were women; 86% were people living with OP, and the remaining 14% included caregivers and fitness instructors): Preserving quality of life and well-being. Preventing fracture related death Preventing admission to long-term care Preserving ability to perform daily activities Preventing all fractures related to osteoporosis Avoiding serious side-effects from drugs A survey in exercise professionals revealed similar priorities. Our working group of researchers, clinicians and a patient advocate used this information to identify the following outcomes as critical when making decisions about exercise: - mortality and fracture-related mortality - hip fractures and other fragility fractures - function and disability - quality of life - fall related injuries (or falls) - the potential for serious harm Non-serious adverse events were identified as important, but not critical outcomes. Bone mineral density was considered an indirect outcome related to hip or other fragility fractures when data on fractures were not available, but it was not a critical or important outcome on its own.	We believe we have captured the main outcomes that people value. However, patients may value the desirable and undesirable effects differently, and their values may change over time, or as their circumstances change. The majority of patients would likely place a high value on a potential reduction in fall or fracture risk and related disability or mortality, or improvement in quality of life or physical functioning, and accept a potential small increase in risk of minor adverse events. Some people may overlook a lack of information on harms if there is a small potential for benefit. There may be a proportion of patients who might not be willing or able to accept potential risks e.g., low physical capacity, social/emotional barriers, high fall or fracture risk. People who are fearful of fractures, falls or adverse events may be concerned if information about risks is uncertain.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The undesirable effects are trivial, although generally not well captured. The balance is weighed towards the small or moderate benefits.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Initiation of resistance training may require formal instruction, particularly in someone at risk of fracture. However, it may be possible to initiate independently using online resources or books. Therefore, there may be a cost, or concerns with access which could create health inequity, which may be greater for those at high risk of fracture, those with low exercise self-efficacy or who fear falls or fractures, who may not feel comfortable with an unsupervised approach.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No	Adherence to progressive resistance training in research studies ranges from 84-91%.	Many of the studies used centre-based

○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Multimodal home exercise may result in low long-term adherence. Giangregorio et al (2018) reported an average adherence of 66% at twelve months. Bennell et al (2010) reported excellent adherence to sessions in clinic with a physical therapist, but larger variability (34%-100%) in self-reported adherence to home exercise. Facilitators of strength training may include (Burton et al, 2017, Burton et al 2017): preventing deterioration (disability), reducing risk of falls, building (toning) muscles, feeling more alert, to feel good physically and mentally, and better concentration. Discussing exercise with a health care provider was reported as influencing participation. Barriers to engaging people in resistance training include pain, injury, illness, perceptions that they might become too muscular, or thinking resistance training increased the risk of having a heart attack, stroke, or death (Burton et al, 2017, Burton et al 2017). A qualitative study among 56 people who discontinued structured resistance training programs for older adults indicated that injury, illness, and taking vacation were the main reasons they ceased participation. Some (11%) respondents said that they were not provided with enough support during the program (Burton et al 2017).	programs. The time commitment and cost required to participate in structured programs may be barriers. The level of instruction and support may influence acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	<u>Cost-effectiveness data in people with vertebral fractures</u> A study by Barker et al (ASBMR abstract 2018) revealed that for people with symptomatic vertebral fractures, seven sessions with a physical therapist to get advice on home exercise was not more cost-effective than a single one-hour session with a physical therapist; interventions that lead to improved adherence to therapy are needed. However, the physical therapy intervention was not progressive resistance training at moderate or high intensity. <u>Cost-effectiveness data from studies in older adults:</u> Patil et al (2016) conducted a two-year RCT in Finland evaluating a multimodal exercise program in women aged 70-80 years living independently, where the exercise included supervised progressive strength training, impact exercise, and balance and agility training delivered in a group setting. They reported a 93% probability that the cost to avoid an injurious fall via participation in exercise was €708 ($1037 Canadian dollars) per person per year. They estimated that there was an 85.6 % chance of the exercise intervention being cost-effective in this population at a willingness to pay €3000 ($4393 Canadian) per injurious fall prevented.	Experience with or knowledge of resistance training, socioeconomic status, baseline risk of fracture and comorbid conditions may influence the feasibility of implementing progressive resistance training. The costs of progressive resistance training depend on the level of need for equipment or instruction. The cost of ~5 sessions with a physical therapist or exercise physiologist is ~$400. It may be more accessible or cost less to attend a class led by other types of exercise professionals or attending small group personal training. Individuals at risk of fracture should consult exercise professionals with training on how to prescribe exercise for people with osteoporosis.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest progressive resistance training ≥ twice weekly, including exercises targeting abdominal and back extensor muscles (GRADE: conditional recommendation, low certainty evidence).

Remark: Resistance training involves exercises where major muscle groups (e.g., upper and lower extremities, chest, shoulders, back) work against resistance (e.g, squats, lunges, and push-ups). Increase volume (e.g., sets, reps, weight), frequency, or difficulty to achieve progressive overload. Many resistance training exercises would be considered functional exercises.

Good practice statement: Activities that involve rapid, repetitive, sustained, weighted, or end-range twisting or flexion of the spine may need to be modified, especially in individuals at high risk of fracture. When available, seek advice from exercise professionals who have training on osteoporosis for exercise selection, intensity and progression, and activity modification, especially after recent fracture or if at high risk of fracture. When not available, refer to Osteoporosis Canada resources.

Justification

Progressive resistance (or strength) training alone may improve quality of life, physical functioning and BMD (very low to moderate certainty evidence), and may reduce mortality (low certainty evidence). Effects on physical functioning are similar in people at high risk of fracture. When combined with functional strength and balance training in older adults, it can reduce the number of falls and people who fall (moderate certainty evidence). Effects on fractures are unknown (very low certainty evidence). Progressive resistance training may need to be performed at moderate-high intensity, and combined with other types of training, to observe changes in BMD. A minimum frequency of twice weekly was included because it was the average frequency used in the studies reviewed, and it is consistent with the Canadian 24-Hour Movement Guidelines. Evidence for strength training alone is of low certainty overall, but evidence for functional training is of moderate certainty. Therefore, we have placed emphasis on recommending functional training for all individuals, acknowledging that there is overlap between functional training and strength or resistance training. Some people may value progressing from functional to strength training or replacing functional with strength training.

Subgroup considerations

We suggest that individuals at high risk of fracture participate in exercise programs that combine progressive resistance training with functional and balance training. Positive effects on physical functioning of a home strength and balance training intervention have been observed in individuals with vertebral fractures (Gibbs et al, 2019). One study reported that resistance and balance training post hip fracture resulted in lower assistive device or nursing home use, but the sample size was small (Singh et al).

Implementation considerations

Progressive resistance training can be delivered using a variety of modes (e.g., body weight exercises, free weights, machines). Progressive resistance training interventions in research studies involve having an exercise professional (e.g., clinical exercise physiologist, physical therapist) select exercises that will provide sufficient overload, provide coaching on alignment or technique and guide progression, in individual or group settings, and based on an assessment of an individual's capabilities. Guidance on exercise selection and proper form may affect the safety and efficacy of, and adherence to progressive resistance training interventions, particularly for individuals at high risk of fracture; one study suggested that a supervised exercise program was more effective (Cergel et al 2019) than home exercise. All exercise programs should consider appropriate warm-up and cool-down activities, and consideration of breathing, alignment and safety precautions.

Monitoring and evaluation

After implementation of the guidelines, it would be useful to evaluate:
- patient's and provider's understanding and acceptability of progressive resistance training, and barriers to and facilitators of resistance training among individuals at risk of fracture
- the harms of resistance training
- the proportion of individuals at risk of fracture (and those at high risk) who participate in progressive resistance training at the population level

Research priorities

- Does progressive resistance training reduce fracture risk in individuals at risk of fractures (e.g., trials with fractures as primary outcome)?
- Does progressive resistance training need to be performed at high intensity, or is moderate intensity resistance training effective for improving physical functioning and quality of life, or reducing fall or fracture risk in individuals at risk of fractures?
- Is progressive resistance training effective on its own (i.e., when not in combination with impact exercise or balance training)?
- What are the harms of progressive resistance training in individuals over the age of 50 who are at increased risk of fracture?
- How can we effectively implement and scale up research on progressive resistance training in the real world? What are the perspectives of people at risk of fracture when it comes to progressive resistance training?
- Are there gender differences in the efficacy or the implementation of progressive resistance training?

QUESTION 4: SHOULD YOGA VS. NO INTERVENTION BE USED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER AT INCREASED RISK OF FRACTURE?

Should yoga vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture (Updated Aug 2021)?	
POPULATION:	Postmenopausal females and males 50 years and older at increased risk of fracture (Updated Aug 2021)
INTERVENTION:	yoga
COMPARISON:	no intervention
MAIN OUTCOMES:	Health Related Quality of Life - Perceived Mental Health; Health Related Quality of Life - Perceived Physical Health; Health Related Quality of Life; Physical Functioning; Function and Disability Balance as indirect measure of falls; Fragility Fractures; Non-Serious Adverse Events; Serious Adverse Events; Pain; Adverse Events.
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	We are updating the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada (section on exercise) as well as the Too Fit to Fracture Recommendations.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low bone strength can increase the risk of bone fractures. One in three women and one in five men over the age of 50 will experience a fracture due to low bone strength. Fractures can cause pain or impaired mobility. Exercise is often recommended to prevent falls and fractures among individuals with low bone mass. Patient preference is an important consideration when recommending options to manage osteoporosis. Things that may influence preferences include interests, current fitness activities or practices, community-based resources, or the opportunity for social or community engagement. Yoga practice is a popular type of physical activity. A recent survey among >1100 patient members of the Canadian Osteoporosis Patient Network revealed that some patients have questions about whether yoga is safe, or effective for improving health outcomes or preventing falls and fractures; 7% of 360 respondents who identified specific questions they had mentioned yoga. Therefore, we sought to understand what was known about yoga for individuals at risk of fracture.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We conducted a systematic review of randomized controlled trials, observational studies, and case series of yoga in people with low bone mass (Kim et al, 2022); we included all study types as we expected the number of studies to be very low. There is one randomized controlled trial of yoga in people with low bone mass, and there are 5 pre-post studies and two case series with overlap in cases. We also searched for systematic reviews of RCTs of yoga in older adults. For health-related quality of life, function and disability, balance (indirect measure of fall risk) and non-serious adverse events, we used data from a systematic review of yoga for older adults by Sivaramakrishnan et al (2019), using pooled data from 9 studies for QoL-mental health, 5 studies for QoL-physical health, 5 studies for walking speed, and 7 studies for balance.	We are interpreting effect size as follows: Small 0.2 Medium 0.5 Large 0.8 Very Large 1.3 Many of the studies where positive effects were observed have been conducted in older adults, and not in people at risk of fracture. It is possible that the information on benefits and harms may not be

Desirable effects:

Physical functioning and Quality of Life: Yoga may have a moderately sized, positive effect on HRQoL (SMD 0.6 SD higher, 95% CI 0.33 to 0.87, 508 participants, moderate certainty evidence). Effects of yoga on walking speed among older adults are uncertain (SMD 0.38 SD higher, 95% CI 0.02 lower to 0.78 higher, 410 participants, low certainty evidence). In addition, positive effects on lower limb strength (effect size 0.45, 95%CT 0.22-0.68, 7 studies) were reported. Uncontrolled studies in individuals at risk of fracture report similar findings. One RCT reported small improvements in Barthel Index with upper body yoga compared to control. Two pre-post studies observed a positive effect of yoga on QoL, as measured by NHP (n=12) and QUALEFFO-41 (n=13), and on function and disability, as measured by TUG scores (n=12) and a neuromuscular battery test (n=13) (Yagli, 2012 & Tuzun, 2010).

Falls, Fractures, Mortality: The effects of yoga on mortality, fracture incidence and falls are uncertain. Yoga may improve balance in older adults (SMD 0.7 SD higher, 95% CI 0.19 higher to 1.22 higher, 265 participants, very low certainty evidence).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with yoga
Health Related Quality of Life - Perceived Mental Health	508 (9 RCTs)	⨁⨁⨁◯ MODERATE[a]	-	The mean health Related Quality of Life - Perceived Mental Health was **0** SD	SMD **0.6 SD higher** (0.33 higher to 0.87 higher)
Health Related Quality of Life - Perceived Physical Health	354 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	-	The mean health Related Quality of Life - Perceived Physical Health was **0** SD	**0.61 SD higher** (0.29 higher to 0.94 higher)
Physical Functioning assessed with: Walking Speed	410 (5 RCTs)	⨁⨁◯◯ LOW[a,b]	-	The mean physical Functioning was **0** SD	SMD **0.38 SD higher** (0.02 lower to 0.78 higher)
Balance as indirect measure of falls	265 (7 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean balance as indirect measure of falls was **0** SD	SMD **0.7 SD higher** (0.19 higher to 1.22 higher)
Fragility Fractures	10 (2 observational studies)	⨁◯◯◯ VERY LOW[b,d,e,f,g]	-	Case series (n=10) reported vertebral compression fractures may be related to yoga practice. No fractures attributable to yoga in RCTs or uncontrolled studies.	

a. Substantial heterogeneity
b. Small effect, small sample size or wide CI
c. Outcome is indirect (e.g., balance is an indirect measure of

generalizable to all people at risk of fracture, such as individuals with a history of vertebral or non-vertebral fractures. There are different types of yoga and some forms may present more risk or benefit than others. The pre-post studies conducted in people with osteoporosis were designed to limit spinal flexion.

fall risk, BMD indirect measure of hip fracture), or population is indirect (e.g., older adults, not people at risk of fracture)

d. Downgrade for observational or case series study design or risk of bias, e.g., incomplete follow-up, inconsistent or flawed measurement of exposure or outcome, failure to control confounding
e. Incomplete follow-up, inappropriate eligibility criteria, no adequate control, inconsistent intervention, flawed measurement of exposure and outcome, or failure to adequately control confounding.
f. Difficult to confirm that vertebral compression fractures were attributable to yoga, or determine absolute risk.
g. May be differential outcome surveillance as it is reported only in intervention group. Few events.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
○ Trivial
● Varies
○ Don't know

RESEARCH EVIDENCE

We conducted a systematic review of randomized controlled trials, observational studies, and case series of yoga in people with low bone mass (Kim et al 2022); we included all study types as we expected the number of studies to be very low. There is one randomized controlled trial of yoga in people with low bone mass, and there are 5 pre-post studies and two case series with overlap in cases. We also searched for systematic reviews of RCTs of yoga in older adults. For non-serious adverse events, we used data from a systematic review of yoga for older adults by Sivaramakrishnan et al (2019).

Undesirable effects: In studies of individuals with osteoporosis, serious adverse events have not been reported, but adverse event reporting in existing research is inadequate (very low certainty evidence). One RCT and three observational studies reported no adverse events directly related to the study intervention. One RCT and one observational study did not mention anything regarding adverse events. Two published case series reports describe vertebral fractures (n=10) that were attributed to spinal flexion poses during yoga. However, we cannot determine the absolute risk. In the systematic review by Sivaramakrishnan et al (2019), four of 24 studies reported no adverse events, and four of 24 studies reported minor events such as groin, fall during yoga session and musculoskeletal pain.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with yoga
Non-Serious Adverse Events	671 (8 RCTs)	⨁◯◯◯ VERY LOW[a,b]	-	Four studies reported adverse events in the yoga group (groin muscle strain, fall during yoga, musculoskeletal pain). Four studies reported no adverse events during yoga.	
Serious Adverse Events	671 (8 RCTs)	⨁◯◯◯ VERY LOW	-	No serious adverse events were reported, but reporting was inadequate.	

ADDITIONAL CONSIDERATIONS

We think there is potential for risk because of the case series and practice-based knowledge of the effects of spinal flexion on fracture, but the supporting evidence is uncertain. The potential for harm will likely vary based on the person's risk level, exercises performed (e.g., presence of flexion/torsion, adequately tailored balance challenges), the instructor and the intensity.

a. May be differential outcome surveillance as it is reported only in intervention group. Few events.
b. Population is indirect (older adults not people with osteoporosis)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	For many critical outcomes, the certainty is low or very low. We know very little about the potential harms. However for quality of life, the evidence is of moderate quality.	

Outcomes	Importance	Certainty of the evidence (GRADE)
Health Related Quality of Life - Perceived Mental Health	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Health Related Quality of Life - Perceived Physical Health	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Physical Functioning assessed with: Walking Speed	CRITICAL	⨁⨁◯◯ LOW[a,b]
Balance as indirect measure of falls	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Fragility Fractures	CRITICAL	⨁◯◯◯ VERY LOW[b,d,e,f,g]
Non-Serious Adverse Events	IMPORTANT	⨁◯◯◯ VERY LOW[g,h]
Serious Adverse Events	CRITICAL	⨁◯◯◯ VERY LOW

a. Substantial heterogeneity
b. Small effect, small sample size or wide CI
c. Outcome is indirect (e.g., balance is an indirect measure of fall risk, BMD indirect measure of hip fracture), or population is indirect (e.g., older adults, not people at risk of fracture)
d. Downgrade for observational or case series study design or risk of bias, e.g., incomplete follow-up, inconsistent or flawed measurement of exposure or outcome, failure to control confounding
e. Incomplete follow-up, inappropriate eligibility criteria, no adequate control, inconsistent intervention, flawed measurement of exposure and outcome, or failure to adequately control confounding.
f. Difficult to confirm that vertebral compression fractures were attributable to yoga or determine absolute risk.
g. May be differential outcome surveillance as it is reported only in intervention group. Few events.
h. Population is indirect (older adults not people with osteoporosis)

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The following outcomes were selected as a priority by >75% of respondents to a survey of 1108 members of the Canadian Osteoporosis Patient Network (96% were women; 86% were people living with OP, and the remaining 14% included caregivers and fitness instructors): Preserving quality of life and well-being. Preventing fracture related death Preventing admission to long-term care Preserving ability to perform daily activities Preventing all fractures related to osteoporosis Avoiding serious side-effects from drugs A survey of exercise professionals revealed similar priorities. Our working group of researchers, clinicians and a patient advocate used this information to identify the following outcomes as critical when making decisions about exercise: - mortality and fracture-related mortality - hip fractures and other fragility fractures - function and disability - quality of life - fall related injuries (or falls) - the potential for serious harm Non-serious adverse events were identified as important, but not critical outcomes. Bone mineral density was considered an indirect outcome related to hip or other fragility fractures when data on fractures were not available, but it was not a critical or important outcome on its own.	We believe we have captured the main outcomes that people value. However, different patients may value the desirable and undesirable effects differently, and their values may change over time, or as their circumstances change. Some people may overlook a lack of information on harms if there is a small potential for benefit. There may be a proportion of patients who might not be willing or able to accept potential risks e.g., low physical capacity, social/emotional barriers, high fall or fracture risk. People who are fearful of fractures, falls or adverse events may be concerned if information about risks is uncertain.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	Yoga may improve physical functioning, and quality of life in older adults, but there is little evidence in people at risk of fracture (very low certainty evidence). The risk appears to be low, but there is little information on harms. It is possible that the harms may vary across types of yoga, or among people of different abilities or fracture risk.	We think there is potential for risk because of the case series and practice-based knowledge of the effects of spinal flexion on fracture, but the supporting evidence is uncertain. The potential for harm will likely vary based on the person's risk level and physical capacity, poses performed (e.g., presence of flexion/torsion, adequately tailored balance challenges), the instructor and the intensity. All the existing RCTs were conducted in older adults, not in people with low bone mass. We hypothesize that the desirable effects on HRQoL and balance observed in older adults would not be different in individuals at moderate to high risk of fracture

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Initiation of yoga may require formal instruction, particularly in someone at risk of fracture. Therefore, there may be a cost, or concerns with access which could create health inequity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	In observational studies or the one RCT of yoga in individuals with low bone mass, adherence was poorly reported or variable, ranging from 5.8% to 100%. In randomized controlled trials among older adults in general (i.e., not specific to people at risk of fracture), the adherence ranged from 63% to 95%.	Some patients will feel strongly that yoga is acceptable whereas others may find it not acceptable. Yoga can include twists and forward flexion, often to end range of motion, or involve postures that place stress on joints, which may deter people from participating.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	There are no studies of the cost-effectiveness of yoga in older adults.	A yoga class costs $10-$23 per class. It is possible to perform yoga at home with minimal to no equipment but may be difficult to adapt safely without instruction. The adherence to, and benefits and harms of yoga may vary with a person's perceptions of yoga, their physical capacity, the available resources, level of instruction and the instructor's qualifications or delivery style or setting (e.g., home vs. community). It may be necessary to ensure that any program or instructor are delivering yoga at a comparable dose and intensity as in studies that demonstrated benefits. In general, yoga would be feasible to implement. However, implementing yoga adapted for osteoporosis by a knowledgeable instructor may be more difficult.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	**Varies**	Don't know

	JUDGEMENT						
			the comparison				
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Individuals who want to participate in other activities (e.g., yoga) for enjoyment or other benefits should be encouraged to do them, if they can be done safely or modified for safety (GRADE: conditional recommendation, very low certainty evidence). Other activities should be encouraged in addition to, but not instead of, balance, functional, and resistance training.

Remark: Encourage a variety of types and intensities of physical activity in accordance with the Canadian 24-Hour Movement Guidelines (https://csepguidelines.ca), such as getting ≥ 150 minutes of moderate to vigorous physical activity, but prioritize balance, functional, and resistance training.

Good practice statement: Activities that involve rapid, repetitive, sustained, weighted, or end range of motion twisting or flexion of the spine may need to be modified, especially in individuals at high risk of fracture. When available, seek advice from exercise professionals who have training on osteoporosis for exercise selection, intensity and progression, and activity modification, especially after recent fracture or if at high risk of fracture. When not available, refer to Osteoporosis Canada resources.

Justification

There is very low certainty evidence that yoga may improve balance or functional mobility, and moderate quality evidence that it may improve quality of life in older adults. There is very little evidence in people with low bone mass. The undesirable effects are somewhat uncertain, and it is possible that the harms may vary across types of yoga or poses, or among people of different abilities or level of fracture risk. Therefore, the balance between benefit and harm may vary.

Subgroup considerations

We planned to do subgroup analyses in individuals with vertebral fractures but there was insufficient evidence to do so.

Implementation considerations

Health care professionals who are developing a physical activity plan with individuals at risk of fracture should encourage continued participation in the types of exercise/physical activity that the patient currently enjoys or practices while also recommending the types of exercise that have the strongest evidence for efficacy and balance between benefit and harms. Individuals at risk of fracture who have a strong preference for yoga can try it or continue to do it but should not be encouraged to do it to the exclusion of types of exercise that have stronger evidence for efficacy. We suggest that people at risk of fracture who want to do yoga consider consulting an instructor knowledgeable about osteoporosis on whether and how to adapt their yoga practice, including avoiding/adapting certain poses, and taking precautions to minimize falls. Knowledge tools that help patients or health care providers have conversations with instructors about how to adapt yoga for osteoporosis would be helpful. Yoga teachers or people at risk of fracture who are practicing yoga should consider adapting yoga poses to avoid rapid, repetitive, weighted, or sustained spinal flexion or torsion, particularly at the end range of motion. Example poses that may be risky include: spinal rocking, ragdoll, saw, plow, pigeon. In addition, yoga teachers or people at risk of fracture who are practicing yoga should take precautions to minimize falls, e.g., using a support object, or modifying activities that challenge balance if they are too difficult. Warm-up and cool-down activities are important, as are consideration of breathing, alignment and safety precautions.

Monitoring and evaluation

Surveillance of adverse events occurring during yoga would be useful to help alleviate patient or health care provider fears, or identify yoga poses or practices that should be avoided or modified.

Research priorities

Future RCTs of yoga in older adults should keep track of falls and fractures and should consider subgroup analyses among individuals with osteoporosis. It may be useful to study the comparative efficacy of yoga and functional strength and balance training, to determine if yoga is a potential alternative to exercise programs that have stronger efficacy for fall prevention. Qualitative research that aims to understanding patient, health care provider or yoga teacher voices or perspectives on implementing these recommendations would be useful in informing future guidelines and implementation.

QUESTION 5: SHOULD PILATES VS NO INTERVENTION BE USED POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER AT INCREASED RISK OF FRACTURE?

Should Pilates vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?	
POPULATION:	Postmenopausal females and males aged 50 years and older at increased risk of fracture
INTERVENTION:	Pilates
COMPARISON:	no intervention
MAIN OUTCOMES:	Health Related Quality of Life; Physical Functioning; Physical Functioning (Systematic Review); Falls; Lumbar Spine BMD (surrogate for fragility fracture); Hip Fractures (or hip/femoral neck BMD); Adverse Events; Mortality;
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	We are updating the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada (section on exercise) as well as the Too Fit to Fracture Recommendations.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low bone strength can increase the risk of bone fractures. One in three women and one in five men over the age of 50 will experience a fracture due to low bone strength. Fractures can cause pain or impaired mobility. People who have hip or vertebral fractures are more likely to die prematurely, often because of fracture-related complications. Exercise is often recommended to reduce fracture risk, but there are many types of exercise. Patients should be encouraged to perform regular physical activities that they enjoy for overall health benefits, consistent with national physical activity guidelines. When it comes to discussions with patients on participating in physical activity to reduce fracture risk, guidelines should emphasize the types of exercise that have a favorable ratio of benefits relative to harms. Pilates is a method of training that emphasizes flexibility, postural alignment, core strength, balance and muscular strength and endurance. There is also a strong focus on breathing patterns, concentration, and flow during movement. There are various approaches to Pilates. For example, clinical Pilates refers to a modified form, where a physical therapist adapts Pilates exercises to address or rehabilitate injuries or other health concerns. Many of the areas of emphasis in the practice of Pilates align with therapeutic goals for people with osteoporosis (e.g., postural alignment, balance). We sought to review the evidence on the potential benefits and harms of Pilates in individuals over the age of 50 who are at risk of fracture.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We led a systematic review to identify studies of Pilates in individuals at risk of fracture (McLaughlin et al, 2022). There are three quasi-RCTs and two case reports examining the benefits or harms of Pilates in people at risk of fractures. We also identified a systematic review and meta-analysis of RCTs of Pilates in older adults (Moreno-Segura et al, 2018) for the physical functioning outcome (5 studies, Timed Up and Go as outcome). However, we had to retrieve the original studies and redo the analyses, and we included only four of the studies, as there appears to be an error in referencing or data extraction with one of the studies included in the systematic	

review.

Desirable Effects

Mortality: There are no trials that report mortality as an outcome.

Falls, Fractures and Bone Mineral Density (BMD): The effects on falls, fragility fractures, hip fractures or mortality are unknown. One study reported positive effects on lumbar spine BMD (MD 0.06 g/cm^2, 95% CI 0.01 higher to 0.11 higher, 41 participants, very low certainty evidence).

Physical functioning and Quality of Life: There is low certainty evidence of small positive effects of Pilates on HRQoL, both mental and physical domains. In addition to the two pooled studies that examined effects of Pilates on QUALEFFO-41 total scores, another study by Angin et al (2015) reported QUALEFFO-41 subscales only, demonstrating small to moderate (effect sizes for the domains range from 0.33-0.63, n=41) in each of the quality of life domains following the Pilates intervention. We found one trial that suggests that Pilates may improve physical functioning (Timed Up and Go MD 1.44 seconds lower, 95% CI 2.04 lower to 0.84 lower, 40 participants, low certainty evidence). That finding is consistent with findings from 4 trials in older adults (Timed Up and Go MD 1.23 seconds lower, 95% CI, 2.3 lower to 0.15 lower, 143 participants, low certainty evidence).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with Pilates
Health Related Quality of Life assessed with: QUALEFFO-41; Scale from 0-100 follow up: range 6 weeks to 12 months	100 (2 RCTs)	⨁⨁◯◯ LOW[a,b,c,d]	-	The mean health Related Quality of Life was **33.6** units	MD **13.8 units lower** (26.16 lower to 1.44 lower)
Physical Functioning assessed with: Timed Up and Go (TUG) follow up: 6 weeks	40 (1 RCT)	⨁⨁◯◯ LOW[b,d]	-	The mean physical Functioning ranged from **7-12** seconds	MD **1.44 seconds lower** (2.04 lower to 0.84 lower)
Function and Disability (Systematic Review) assessed with: Timed Up and Go (TUG) follow up: range 4 weeks to 12 weeks	143 (4 RCTs)	⨁⨁◯◯ LOW[d,e]	-	The mean function and Disability (Systematic Review) ranged from **7-12** seconds	MD **1.23 seconds lower** (2.3 lower to 0.15 lower)
Falls assessed with: Self-reported number of fallers follow up: 12 months	60 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,d]	-	2 falls in Pilates group (n=30) vs. 3 in control (n=30).	

Lumbar Spine BMD (surrogate for fragility fracture) follow up: 6 months	41 (1 RCT)	⨁◯◯◯ VERY LOW[a,b,d,f,g]	-	The mean lumbar Spine BMD (surrogate for fragility fracture) was **0.653** g/cm^2	MD **0.06 g/cm^2 higher** (0.01 higher to 0.11 higher)
Hip Fractures (or hip/femoral neck BMD) - not reported	-	-	-	-	-
Mortality - not reported	-	-	-	-	-

1. Küçükçakir, N.,Altan,L.,Korkmaz,N.. Effects of Pilates exercises on pain, functional status and quality of life in women with postmenopausal osteoporosis. Journal of Bodywork & Movement Therapies; 2013.

a. "Intention-to-treat" analysis was not used, which could result in overestimation or underestimation of effect.
b. Allocation of groups is not adequately concealed
c. There is substantial heterogeneity, which likely can be explained by differences in length of intervention
d. Small sample size
e. Heterogeneity is substantial to considerable: I^2=76%
f. BMD is a surrogate measure of fragility fracture.
g. Outcome assessors not adequately blinded to experimental groups

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	We led a systematic review to identify studies of Pilates in individuals at risk of fracture (McLaughlin et al, 2022). There are three quasi-RCTs and two case reports examining the benefits or harms of Pilates in people at risk of fractures. We also identified a systematic review and meta-analysis of RCTs of Pilates in older adults (Moreno-Segura et al, 2018) for the physical functioning outcome (5 studies, Timed Up and Go as outcome). However, we had to retrieve the original studies and redo the analyses, and we included only four of the studies, as there appears to be an error in referencing or data extraction with one of the studies included in the systematic review. **Undesirable Effects:** Adverse events are not reported on in the trials we reviewed, nor in the systematic review of Pilates in older adults, therefore the potential for harms is unknown.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	For several outcomes there are no included studies. For other outcomes the certainty is low or very low.	

Outcomes	Importance	Certainty of the evidence (GRADE)
Health Related Quality of Life assessed with: QUALEFFO-41; Scale from 0-100 follow up: range 6 weeks to 12 months	CRITICAL	⨁⨁◯◯ LOW[a,b,c,d]
Physical Functioning assessed with: Timed Up and Go (TUG) follow up: 6 weeks	CRITICAL	⨁⨁◯◯ LOW[b,d]
Function and Disability (Systematic Review) assessed with: Timed Up and Go (TUG) follow up: range 4 weeks to 12 weeks	CRITICAL	⨁⨁◯◯ LOW[d,e]
Falls assessed with: Self-reported number of fallers follow up: 12 months	CRITICAL	⨁◯◯◯ VERY LOW[a,d]
Lumbar Spine BMD (surrogate for fragility fracture) follow up: 6 months	CRITICAL	⨁◯◯◯ VERY LOW[a,b,d,f,g]
Hip Fractures (or hip/femoral neck BMD) - not reported	CRITICAL	-
Adverse Events - not reported	CRITICAL	-
Mortality - not reported	CRITICAL	-

a. "Intention-to-treat" analysis was not used, which could result in overestimation or underestimation of effect.
b. Allocation of groups is not adequately concealed
c. There is substantial heterogeneity, which likely can be explained by differences in length of intervention
d. Small sample size
e. Heterogeneity is substantial to considerable: I^2=76%
f. BMD is a surrogate measure of fragility fracture.
g. Outcome assessors not adequately blinded to experimental groups

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The following outcomes were selected as a priority by >75% of respondents to a survey of 1108 members of the Canadian Osteoporosis Patient Network (96% were women; 86% were people living with OP, and the remaining 14% included caregivers and fitness instructors): Preserving quality of life and well-being. Preventing fracture related death Preventing admission to long-term care Preserving ability to perform daily activities Preventing all fractures related to osteoporosis Avoiding serious side-effects from drugs A survey in exercise professionals revealed similar priorities. Our working group of researchers, clinicians and a patient advocate used this information to identify the following outcomes as critical when making decisions about exercise: - mortality and fracture-related mortality	How people feel about doing Pilates may modify how people value the main outcomes. Patients place the highest value on physical functioning, quality of life, and preventing fractures and fracture-related disability or mortality. We believe we have captured the main outcomes that people value. However, different patients may value the desirable and undesirable effects differently, and their values may change over time, or as their circumstances change. Most patients would likely place a high value on a potential reduction in fall or fracture risk and related disability or

	- hip fractures and other fragility fractures - function and disability - quality of life - fall related injuries (or falls) - the potential for serious harm Non-serious adverse events were identified as important, but not critical outcomes. Bone mineral density was considered an indirect outcome related to hip or other fragility fractures when data on fractures were not available, but it was not a critical or important outcome on its own.	mortality, or improvement in quality of life or physical functioning, and accept a potential small increase in risk of minor adverse events. Some people may overlook a lack of information on harms if there is a small potential for benefit. There may be a proportion of patients who might not be willing or able to accept potential risks e.g., low physical capacity, social/emotional barriers, high fall or fracture risk. People who are fearful of fractures, falls or adverse events may be concerned if information about risks is uncertain.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	There is a small potential for improvement in HRQoL and physical functioning (low certainty evidence). There are several outcomes (fragility fractures, hip fractures, falls, mortality) where the effects are unknown. We do not know whether there are potential harms. We have very few studies to use in decision-making about the balance between desirable and undesirable effects.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		We suggest formal instruction by credentialed Pilates instructors who also have expertise in osteoporosis, particularly for someone at risk of fracture. Therefore, there may be a cost, or concerns with access which could create health inequity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	In the three Quasi-RCTs of Pilates in people with low bone mass, no data on adherence were reported. Among studies of Pilates in older adults, adherence was either not reported, or ranged from 75-100%. Five of 360 respondents (1.2%) to an open-ended question in our survey of the Canadian Osteoporosis Patient Network voiced questions about the safety or efficacy of Pilates, suggesting that they are considering it as an acceptable intervention and want information for decision-making.	Health care providers might be concerned about access, transportation, and cost, and how to identify reputable Pilates providers. Some patients or health care providers might be concerned about the unknown harms. There are various approaches to Pilates (e.g., Stott, clinical), and the types available may vary by community. Some people may not like Pilates, or the lack of autonomy in initiating it e.g., having to go to or pay for a class to have an initial postural assessment and learn the foundational principles. On the other hand, some people may prefer to attend a class because of the social context and the access to instruction. They may also appreciate that the goals of Pilates include a focus on muscular strength, balance, and posture, which are relevant for people with osteoporosis. Pilates can be done at home once one acquires the necessary strength and precision. However, attending a class or

		session of classes over the years may be necessary for postural re-assessment, or to ensure good practice. Physical therapists who are trained Pilates instructors would find it acceptable to include Pilates as part of osteoporosis management. Some people have extended health insurance that might cover Pilates instruction by a physical therapist. The time commitment required to participate in structured programs may be a barrier, especially if people are working or have other demands on their time. Therefore, the acceptability of Pilates would vary among health care providers and patients, depending on preference, access, cost, their baseline risk of fracture, and how they value the benefits and harms.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	There are no studies of the cost-effectiveness of Pilates in older adults with low bone mass, or in older adults.	The adherence to, and benefits and harms may vary with environment, level of instruction and qualifications of instructor. Many of the studies were delivering clinical Pilates (i.e., delivered by a physical therapist often tailored for a specific clinical indication). To achieve the same benefits, it may be necessary to include similar Pilates movements. The cost to attend a Pilates class (drop-in) is $18-25. For home exercise, the cost of equipment are as follows: - $10-20 for a mat - $10-15 for bands - $5-10 for a ball It is estimated that, if one needed instruction, the most cost-efficient way to begin a Pilates practice would be to attend a class twice weekly for ~6 months to learn technique (~$1050), and purchase equipment at home for continued practice ($25): total cost $1075. It may be necessary to continue attending classes intermittently to ensure good technique and progress exercises (~$22 per class).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Individuals who want to participate in other activities (e.g., Pilates) for enjoyment or other benefits should be encouraged to do them, if they can be done safely or modified for safety (GRADE: conditional recommendation, very low certainty evidence). Other activities should be encouraged in addition to, but not instead of, balance, functional, and resistance training.

Remark: Encourage a variety of types and intensities of physical activity in accordance with the Canadian 24-Hour Movement Guidelines (https://csepguidelines.ca), such as getting ≥ 150 minutes of moderate to vigorous physical activity, but prioritize balance, functional, and resistance training.

Good practice statement: Activities that involve rapid, repetitive, sustained, weighted, or end range of motion twisting or flexion of the spine may need to be modified, especially in individuals at high risk of fracture. When available, seek advice from exercise professionals who have training on osteoporosis for exercise selection, intensity and progression, and activity modification, especially after recent fracture or if at high risk of fracture. When not available, refer to Osteoporosis Canada resources.

Justification

There is low certainty evidence that Pilates may result in small improvements in quality of life and mobility. Harms attributable to intervention are not evident, but adverse event reporting is non-existent in studies. The data are derived from a limited number of participants.

Subgroup considerations

There is insufficient evidence to support subgroup analyses.

Implementation considerations

The research that we evaluated often used what was called "clinical Pilates", which refers to Pilates delivered by a physical therapist, or in conjunction with a physical therapy program. It is possible that Pilates delivered in conjunction with physical therapy, or by a physical therapist may differ somewhat from other types of Pilates. Therefore, individuals at risk of fracture who wish to practice Pilates because of the potential for improvement in quality of life or physical functioning observed in trials, they might consider Pilates delivered by physical therapist. Knowledge translation tools that help patients have conversations with instructors about how to adapt Pilates for osteoporosis would be helpful. Warm-up and cool-down activities are important, as are consideration of breathing, alignment and safety precautions.

Monitoring and evaluation

Future research and implementation efforts should monitor:
- the understanding and acceptability of Pilates, and the barriers to and facilitators of its implementation for individuals at risk of fracture
- the potential for harms
- costs relative to benefits

Research priorities

Pilates may have similar therapeutic goals to other types of exercise that are often recommended for individuals at risk of fracture e.g., resistance training, postural alignment, balance. Therefore, it would be interesting to see if it is effective compared to control, or non-inferior compared to those types of exercise. Future trials should consider monitoring adverse events in all study arms. Qualitative research that aims to understanding patient, health care provider or Pilates instructor voices or perspectives on implementing exercise recommendations would be useful in informing future guidelines and implementation.

QUESTION 6: SHOULD BALANCE AND FUNCTIONAL EXERCISES VS. NO INTERVENTION BE USED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER AT INCREASED RISK OF FRACTURE?

Should functional and balance training vs. no intervention be used for postmenopausal females and males aged 50 years and older at increased risk of fracture?	
POPULATION:	Postmenopausal females and males aged 50 years and older at increased risk of fracture
INTERVENTION:	functional and balance training
COMPARISON:	no intervention
MAIN OUTCOMES:	All-cause Mortality; Fall-Related Fragility Fractures; Total Hip BMD (surrogate for hip fractures); Number of Falls; Number of people who fall; Physical Functioning; Health Related QoL; Serious Adverse Events; Minor Adverse Events; Fall related injuries;
SETTING:	community
PERSPECTIVE:	Community-dwelling adults over the age of 50
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low bone strength can increase the risk of bone fractures. One in three women and one in five men over the age of 50 will experience a fracture due to low bone strength. Fractures can cause pain or impaired mobility. People who have hip or vertebral fractures are more likely to die prematurely, often as a result of fracture-related complications. Falls are a contributing factor to many osteoporotic fractures. Therefore, preventing falls and improving mobility may reduce fracture risk. Balance and functional training activities are often used as task-specific training for fall prevention in older adults. The ProFaNE taxonomy defines *balance training* as training that "...involves the efficient transfer of bodyweight from one part of the body to another or challenges specific aspects of the balance systems (e.g., vestibular systems). Balance retraining activities range from the reeducation of basic functional movement patterns to a wide variety of dynamic activities that target more sophisticated aspects of balance." Functional training is defined as using "...functional activities as the training stimulusand is based on the theoretical concept of task specificity. (http://www.profane.eu.org/taxonomy.html)." Physical functioning was deemed important to patients in a survey of >1100 members of the Canadian Osteoporosis Patient Network (Funnell et al, 2019). We sought to evaluate the potential benefits and harms of balance and functional training for people over the age of 50 who are at risk of fracture.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We completed a systematic review of randomized controlled trials (RCTs) of balance and functional training activities or exercises in people at risk of fracture and included studies where the intervention aligned with the ProFaNE definition of balance or functional training. In addition, we searched for systematic reviews of balance and functional training interventions in older adults, and identified two systematic reviews (Sherrington et al, 2019, Guirguis-Blake et al, 2018)	

Falls and Fall-related injuries: We used evidence from a 2019 Cochrane review of exercise for preventing falls in older adults because there were not enough sufficiently powered RCTs in people at risk of fracture. There is high certainty evidence that functional and balance training results in a 13% reduction in the risk of being a faller, and a 24% reduction in the rate of falls - see table below (Sherrington et al, 2019). The evidence related to the effects of functional and balance training on fall risk comes from studies that often recruit people with risk factors for falls. However, the effect is not likely to be different in individuals at risk of fracture. The effect on falls requiring medical attention was less certain (RR 0.76, 95% CI 0.54 to 1.09; 583 participants, 3 studies, I^2 = 0%; low-certainty evidence). In addition, combination interventions, most often when strength training is combined with functional and balance training, has a moderate effect, reducing the risk of falls by 34% (RaR 0.66, 95% CI 0.50 to 0.88; 1374 participants, 11 studies; moderate-certainty evidence) and the number of people experiencing one or more falls 22% (RR 0.78, 95% CI 0.64 to 0.96; 1623 participants, 17 studies; moderate-certainty evidence).

Function and Disability: Functional and balance training improves mobility to a small extent (low certainty).

Health-related quality of life: There is low certainty evidence that functional and balance training can improve quality of life.

Fractures: A 2019 Cochrane review reported that functional and balance training reduced the number of people experiencing one or more fall-related fractures by 56% compared with control (RR 0.44, 95% CI 0.25 to 0.76; 2139 participants, 7 studies, I^2 = 0%; low-certainty evidence).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with functional and balance training
All-cause Mortality follow up: range 12 months to 60 months	4263 (11 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]	**RR 0.93** (0.71 to 1.22)	Study population	
				49 per 1,000	**3 fewer per 1,000** (14 fewer to 11 more)
Fall-Related Fragility Fractures	2139 (7 RCTs)	⨁⨁◯◯ LOW[a,d]	**RR 0.44** (0.25 to 0.76)	Study population	
				48 per 1,000	**27 fewer per 1,000** (36 fewer to 12 fewer)
Total Hip BMD (surrogate for hip fractures) follow up: range 8 months to 1 years	271 (3 RCTs)	⨁◯◯◯ VERY LOW[a,b]	-	The mean total Hip BMD (surrogate for hip fractures) was **0.837** SD	SMD **0.09 SD higher** (0.15 lower to 0.33 higher)
Number of Falls	7920 (41 RCTs)	⨁⨁⨁⨁ HIGH[e]	**Rate ratio 0.76** (0.70 to 0.81)	Study population	
				850 per 1,000	**204 fewer per 1,000** (255 fewer to 161 fewer)
Number of	8288	⨁⨁⨁⨁	**RR 0.87**	Study population	

people who fall	(38 RCTs)	HIGH[e]	(0.82 to 0.91)	200 per 1,000	**26 fewer per 1,000** (36 fewer to 18 fewer)
Physical Functioning assessed with: Timed Up and Go Test follow up: range 8 weeks to 1 years	871 (10 RCTs)	⨁⨁◯◯ LOW[a,f]	-[g]	The mean physical Functioning was **9.87** Seconds	MD **1.08 Seconds lower** (1.21 lower to 0.95 lower)[g]
Health Related QoL assessed with: QUALEFFO-41 Total Score- lower is better follow up: range 5.5 weeks to 25 weeks	854 (7 RCTs)	⨁⨁◯◯ LOW[f]	-	The mean health Related QoL was **22.35** Points	MD **2.48 Points lower** (3.64 lower to 1.31 lower)

a. Downgrade 1 level for each source of indirectness: hip BMD is a surrogate outcome for fracture risk, population not people at risk of fracture, or used a multicomponent intervention that included other types of exercise (e.g., resistance training, aerobic physical activity).
b. Mean difference crosses the point of no effect.
c. Trials were assessed using the US Preventive Task Force Quality assessment. The majority of studies receiving a 'fair' rating - downgrade quality of evidence by one level.
d. Trials assessed using the Cochrane Risk of Bias tool resulting in a low certainty of evidence across trials.
e. Although population is older adults and therefore indirect, the effect on falls or being a person who falls is not likely to be different in people at risk of fractures.
f. High heterogeneity in pooled estimates, or variability in direction or magnitude of effect across studies that is unexplained.
g. Minimum meaningful change of 1 second, ranging from 7-30 seconds.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	We completed a systematic review of randomized controlled trials (RCTs) of balance and functional training activities or exercises in people at risk of fracture, and included studies where the intervention aligned with the ProFaNE definition of balance or functional training. In addition, we searched for systematic reviews of balance and functional training interventions in older adults, and identified two systematic reviews (Sherrington et al, 2019, Guirguis-Blake et al, 2018) **Undesirable effects:** Among the RCTs we reviewed no serious or minor adverse events related to functional and balance training were reported. In the systematic review of functional and balance training in older adults (Sherrington, 2019), there were two serious adverse events related to intervention in 4217 participants: inguinal hernia that required surgical repair, and a pelvic stress fracture. The review also reported cases of exercise-related muscle pain or strain, or aggravation of muscle or joint pain. Although the review by Sherrington et al (2019) rated the evidence as very low certainty, we upgraded the rating to moderate because of the large sample size and because the types of events that are reported are minor or transient, and consistent with what would be expected when starting a new exercise program.	

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with functional and balance training
Serious Adverse Events assessed with: Self-reported follow up: range 24 weeks to 1 years	454 (5 RCTs)	⨁⨁⨁◯ MODERATE[a,b]	-	Serious adverse events were either not reported, or infrequent.	
Minor Adverse Events assessed with: Self-reported follow up: range 24 weeks to 1 years	909 (7 RCTs)	⨁⨁⨁◯ MODERATE[a]	-	Exercise-related joint or muscle pain or soreness, or exacerbation of existing joint or muscle pain may occur.	

a. Downgrade 1 level for each source of indirectness: hip BMD is a surrogate outcome for fracture risk, population not people at risk of fracture, or used a multicomponent intervention that included other types of exercise (e.g., resistance training, aerobic physical activity).
b. Low number of studies and of events.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ● Moderate ○ High ○ No included studies	For many outcomes the certainty of the evidence of effects is low or very low. However, we have high certainty evidence for the effects of functional and balance training on the risk of falls or being a faller. The certainty around harms is moderate.	

Outcomes	Importance	Certainty of the evidence (GRADE)
All-cause Mortality follow up: range 12 months to 60 months	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Fall-Related Fragility Fractures	CRITICAL	⨁⨁◯◯ LOW[a,d]
Total Hip BMD (surrogate for hip fractures) follow up: range 8 months to 1 years	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Number of Falls	CRITICAL	⨁⨁⨁⨁ HIGH[e]
Number of people who fall	CRITICAL	⨁⨁⨁⨁ HIGH[e]
Physical Functioning assessed with: Timed Up and Go Test follow up: range 8 weeks to 1 years	CRITICAL	⨁⨁◯◯ LOW[a,f]
Health Related QoL assessed with: QUALEFFO-41 Total Score-lower is better follow up: range 5.5 weeks to 25 weeks	CRITICAL	⨁⨁◯◯ LOW[f]
Serious Adverse Events assessed with: Self-reported follow up: range 24 weeks to 1 years	CRITICAL	⨁⨁⨁◯ MODERATE[a,g]
Minor Adverse Events assessed with: Self-reported follow up: range 24 weeks to 1 years	CRITICAL	⨁⨁⨁◯ MODERATE[a]

a. Downgrade 1 level for each source of indirectness: hip BMD is a surrogate outcome for fracture risk, population not people at risk of fracture, or used a multicomponent intervention that included other types of exercise (e.g., resistance training, aerobic physical activity).
b. Mean difference crosses the point of no effect.
c. Trials were assessed using the US Preventive Task Force Quality assessment. The majority of studies receiving a 'fair' rating - downgrade quality of evidence by one level.
d. Trials assessed using the Cochrane Risk of Bias tool resulting in a low certainty of evidence across trials.
e. Although population is older adults and therefore indirect, the effect on falls or being a person who falls is not likely to be different in people at risk of fractures.
f. High heterogeneity in pooled estimates, or variability in direction or magnitude of effect across studies that is unexplained.
g. Low number of studies and of events.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability	The following outcomes were selected as a priority by >75% of respondents to a survey of 1108 members of the Canadian Osteoporosis Patient Network (96%	Patients place the highest value on physical functioning, quality of life, and fracture-

● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	were women; 86% were people living with OP, and the remaining 14% included caregivers and fitness instructors): Preserving quality of life and well-being. Preventing fracture related death Preventing admission to long-term care Preserving ability to perform daily activities Preventing all fractures related to osteoporosis Avoiding serious side-effects from drugs A survey of exercise professionals revealed similar priorities. Our working group of researchers, clinicians and a patient advocate used this information to identify the following outcomes as critical when making decisions about exercise: - mortality and fracture-related mortality - hip fractures and other fragility fractures - function and disability - quality of life - fall related injuries (or falls) - the potential for serious harm Non-serious adverse events were identified as important, but not critical outcomes. Bone mineral density was considered an indirect outcome related to hip or other fragility fractures when data on fractures were not available, but it was not a critical or important outcome on its own.	related disability or mortality. We believe we have captured the main outcomes that people value. However, different patients may value the desirable and undesirable effects differently, and their values may change over time, or as their circumstances change. Most patients would likely place a high value on a potential reduction in fall or fracture risk and related disability or mortality, or improvement in quality of life or physical functioning, and accept a potential small increase in risk of minor adverse events. Some people may overlook a lack of information on harms if there is a small potential for benefit. There may be a proportion of patients who might not be willing or able to accept potential risks e.g., low physical capacity, social/emotional barriers, high fall or fracture risk. People who are fearful of fractures, falls or adverse events may be concerned if information about risks is uncertain. Fall prevention and improved physical functioning and mobility are tangible things that people would be receptive to. They may be less concerned about potential for harms, or lack of effect on other outcomes given the potential for benefit.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The balance of effects favours the of intervention because there is moderate certainty evidence of infrequent or minor harms and there is a positive, small potential for benefit. Our judgement is weighed heavily by the high certainty evidence that functional and balance training can reduce falls in older adults, which is the intended outcome of that type of exercise. There is also potential for a small improvement in physical functioning and quality of life. We are uncertain about the effects on bone mineral density or fractures.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Access may be easier in larger centres or for people who are more informed and motivated. However, it is an intervention that has been demonstrated to be scalable and can be done at home. Because many of the movements are functional, it may be easy to scale in different languages. Most people would have a fair and equal opportunity to perform functional and balance training. At the societal level it probably has no impact on equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No	Adherence to functional and balance training was documented a number of	

○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	different ways across trials. It ranged from very poor to very good. If an average adherence is calculated across trials it was 82%. Adherence can vary widely across studies (18%-100%) (Shier et al. 2016) and may be higher in supervised, laboratory settings versus the real-world (Morey et al. 2003). Gibbs et al (2019) explored factors that influenced participation in a functional and balance program for older adults. Facilitators included: referral from their physician/nurse; instruction from a physical therapist; or opportunity to improve health and physical functioning, become more active, or prevent falls. Incentives included: free program; ability to join with caregiver/spouse/friend; social support; learn new information; try a new exercise program; low-intensity program; located at physician's clinic; and providing education/training for deliverers of exercise. Barriers included: chronic illness or injury, difficulty understanding the program, limited one-on-one attention, lack of home-based visits, and diversity in participants' goals, intentions, and plans when sessions are delivered in a group. The Otago Exercise Program and other programs that involve functional and balance training (Stepping on, LiFE) have been scaled up to various degrees, providing evidence of acceptability to stakeholders and policy makers.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The Otago Exercise Programme, which is a standardized home-based functional and balance training program (including weighted exercises and dynamic balance exercises) delivered by an exercise professional over 4 home visits, had an estimated cost-effectiveness ratio of £173 at 2008 prices ($280 Canadian dollars, or $331 in 2019 at an annual rate of inflation of 1.54%) per fall prevented. Patil et al (2001) conducted a two-year RCT in Finland evaluating a multimodal exercise program in women aged 70-80 years living independently, where the exercise included supervised progressive moderate intensity (60-75% 1RM) strength training, impact exercise, and balance and agility training delivered in a group setting. They reported a 93% probability that the cost to avoid an injurious fall via participation in exercise was €708 per person per year ($1037 Canadian dollars, or $1184 in 2019 at 1.54% inflation). They estimated that there was an 85.6 % chance of the exercise intervention being cost-effective in this population at a willingness to pay €3000 ($4393 Canadian, or $5015 in 2019) per injurious fall prevented.	It is possible to do functional and balance training with little to no equipment at home (e.g., $10-15 for exercise bands, $15-20 for ankle weights for Otago program), or to attend free or subsidized community-based programs. The costs of functional and balance training can range substantially depending on the level of need for equipment or instruction. If individualized instruction is required, consulting an exercise physiologist or physical therapist for a home program might cost $350 to $400 over 4-5 sessions. The cost can be cheaper if one attends small-group personal training or subsidized or free community-based classes or other services (e.g., falls prevention exercise classes, cardiac rehabilitation, YMCA programs).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

We recommend balance and functional training ≥ twice-weekly to reduce the risk of falls. (GRADE: strong recommendation, moderate certainty evidence).

Remark: Increase difficulty, pace, frequency, volume (sets, reps) or resistance over time. Balance exercises challenge aspects of balance, such as:

- Shifting weight to the limits of stability;
- Reacting to things that upset your balance (e.g., catching- throwing a ball);
- Maintaining balance while moving (e.g., Tai chi, heel raises, agility training);
- Reducing base of support (e.g., standing on one foot).

Functional exercises improve ability to perform everyday tasks, or do activities for fun or fitness (e.g., chair stands for sit-to-stand ability, stair-climbing to train for hiking).

Good practice statement: Activities that involve rapid, repetitive, sustained, weighted, or end range of motion twisting or flexion of the spine may need to be modified, especially in individuals at high risk of fracture. When available, seek advice from exercise professionals who have training on osteoporosis for exercise selection, intensity and progression, and activity modification, especially after recent fracture or if at high risk of fracture. When not available, refer to Osteoporosis Canada resources.

Justification

Balance and functional training reduces falls and has effects on outcomes deemed important to patients (i.e., quality of life, physical functioning). Adverse events are infrequent. Effects on fractures (or bone mineral density) and mortality are less certain. Exercises that target physical function may be appealing and practical. We also placed a high value on the potential feasibility, scalability and acceptability of balance and functional training. We felt it important to provide a recommendation for frequency of training. We do not have comparative efficacy studies examining which frequency is best, so our recommendation of twice weekly reflects the low end of the range of frequency often used in studies informing the guidelines. Interventions ranged in frequency and duration. Most balance and functional interventions targeting falls involved three balance and functional training sessions per week. Tai Chi interventions were typically performed twice weekly. Studies reporting functional outcomes involved an average of three training sessions weekly. National guidelines recommend strength training twice weekly.
**Evidence for strength training alone is of low certainty overall, but evidence for functional training is of moderate certainty. Therefore, we have placed emphasis on recommending functional training for all individuals, acknowledging that there is overlap between functional training and strength or resistance training.*

Subgroup considerations

We considered a separate analysis in individuals with vertebral fractures but there were not enough studies that exclusively studied balance and functional training.

Implementation considerations

All exercise programs should consider appropriate warm-up and cool-down activities, and consideration of breathing, alignment, and safety precautions. The balance and functional training should be delivered at a comparable dose and intensity, with progression, as in the studies that demonstrated benefits. It is uncertain whether balance and functional training will improve bone mineral density or reduce fractures or premature death, therefore it may be important to combine balance and functional training with other types of exercise (e.g., impact or resistance training, or aerobic physical activity) that may have an effect on those outcomes. Combining balance and functional training with other types of exercise, most commonly resistance training, may also have a moderate benefit when it comes to preventing falls

and a small effect on the number of people experiencing one or more falls. Individuals who have gait and balance difficulties, or hyperkyphosis, may be at higher risk of falls, and may want to seek guidance on exercise selection and progression.

Monitoring and evaluation

It would be informative to monitor how health care providers, patients and exercise providers implement balance and functional training among individuals at risk of fractures (or older adults with risk factors for falls and fractures) and evaluate cost-effectiveness. Because there are few trials in individuals at high risk of fracture, we should still monitor harms in clinical trials and implementation studies.

Research priorities

There is a strong need for the development and evaluation of models of delivery for balance and functional training that are acceptable and feasible to implement in a variety of settings and communities, and generalizable to individuals at risk of fracture. Pragmatic research examining how to effectively implement and scale up balance and functional training among adults at risk of fracture is an important priority. Pragmatic research should also consider being inclusive of individual at high risk with other comorbidities such as stroke, Parkinson's or other neuromuscular or musculoskeletal disorders.

QUESTION 7: SHOULD EXERCISE TARGETING BACK EXTENSOR MUSCLES, CORE STABILITY OR POSTURE VS. NO INTERVENTION BE USED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER WITH HYPERKYPHOSIS?

Should exercises targeting back extensor muscles, core stability or posture vs. no intervention be used for postmenopausal females and males aged 50 years and older with hyperkyphosis (and increased fracture risk)?	
POPULATION:	Postmenopausal females and males aged 50 years and older with hyperkyphosis
INTERVENTION:	exercises targeting back extensor muscles, core stability or posture
COMPARISON:	no intervention
MAIN OUTCOMES:	Kyphosis curve; Back extensor strength; Back extensor endurance; Rate of falls; Fall-related injuries; Fragility fractures; Mortality; Physical functioning; Quality of Life; Pain; Serious adverse events; Minor adverse events;
SETTING:	Community-dwelling individuals
PERSPECTIVE:	Population
BACKGROUND:	We are updating the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada (section on exercise) as well as the Too Fit to Fracture Recommendations.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low bone strength can increase the risk of bone fractures. One in three women and one in five men over the age of 50 will experience a fracture due to low bone strength. Fractures can cause pain or impaired mobility. People who have hip or vertebral fractures are more likely to die prematurely, often because of fracture-related complications. Vertebral fractures can contribute to the development of an exaggerated curve in the thoracic spine, or hyperkyphosis, defined as a thoracic spine curvature of at least 40°. Other things that can contribute to hyperkyphosis include degenerative disc disease, poor spine mobility, weakness of the spinal extensors, ankylosing spondylitis and shortening of pectoral and hip flexors muscles. Hyperkyphosis can lead to impaired pulmonary or physical functioning and may increase the risk of new vertebral fractures. Twenty to forty percent of older adults have hyperkyphosis, which is associated with increased mortality independent of bone mineral density (BMD). Exercise programs that target back extensor strength or endurance, as well as other changes in posture, such as forward head posture, shoulder protraction and flattening of lumbar lordosis have previously been recommended for individuals with osteoporosis (Giangregorio et al, 2015), particularly individuals with weakness in muscles contributing to core stability, individuals with hyperkyphosis or individuals who have had vertebral fractures. However, the evidence to support the recommendation was limited (Bansal et al, 2014). We sought to evaluate prior evidence and evidence that has emerged since then to address the question: Should exercises targeting back extensor muscles, core stability or posture be recommended for individuals over the age of 50 with hyperkyphosis, including those who are at risk for fractures?	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial	We updated an existing systematic review (Bansal et al, 2014) exploring the effects	Some interventions (e.g., Bennell et al, 2010,

● Small ○ Moderate ○ Large ○ Varies ○ Don't know	of exercise on hyperkyphosis (Ponzano et al, 2021). We chose to focus on studies targeting hyperkyphosis for several reasons: a) we are updating the 2010 Guidelines, and specifically, we are determining whether to retain the 2010 recommendation for "exercises to enhance core stability and thus to compensate for weakness or postural abnormalities are recommended for individuals who have had vertebral fractures "; b) studies that evaluate the effects of exercise on hyperkyphosis often target people with hyperkyphosis at baseline, to be able to observe a change (no ceiling effect); and c) studies that focus on hyperkyphosis often emphasize the types of exercise of interest, i.e., back extensor muscles, core stability, postural abnormalities. Where possible, we completed subgroup analyses of studies of individuals with vertebral fractures or low bone mass, but participants in these studies may not have had hyperkyphosis at baseline. We identified 24 relevant studies, 11 of which were included in meta-analyses. Watson et al 2019 was included because they examined the effects of high intensity resistance training (including exercises involving thoracic and lumbar extension) combined with impact training in a subgroup (n=51 of 101) of the participants reported in a larger trial (Watson et al 2017) who had low bone mass. In the subgroup analysis, average kyphosis at baseline measured with flexicurve met the criteria for hyperkyphosis, whereas the larger trial (Watson 2017) did not report baseline spinal curvature data. We report data from both trials here but interpret them cautiously because some data are subgroup analyses and some are not, and the intervention was not directly focused on hyperkyphosis, rather it combined high impact and high intensity resistance training with the goal of improving bone mass. However, two of four exercises, deadlift and overhead press, would emphasize strengthening lumbar and thoracic extensors, respectively. **Desirable effects:** **Quality of life:** There is moderate certainty evidence that exercise programs that target back extensor muscles, core stability and posture in individuals with hyperkyphosis can have a small positive effect on quality of life (SMD 0.26 higher, 95% CI 0.10 higher to 0.42 higher, 5 RCTs, 613 participants). Similar findings were observed when the analysis was restricted to individuals with hyperkyphosis who had low bone mass or vertebral fractures (SMD 0.28 higher, 95%CI 0.08 to 0.48 higher, 3 RCTs, 211 participants). **Fall-related injuries, fractures, mortality:** There was insufficient data to make inferences related to the effects of exercise for posture, back extensor muscles or core stability on fall-related injuries, fractures or mortality. Three studies reported on falls, but no effect of exercise was observed when data were pooled (IRR 0.14, 95%CI -0.45 to 0.72, n=537, low certainty evidence). Barker et al 2019 reported 4 fragility fractures in the intervention group (175 participants) and 5 fragility fractures in the control group (173 participants). Watson et al 2019 reported no new spine fractures in the exercise group, and one spine fracture in the control group. Watson et al 2017 reported statistically significant effects of exercise on bone mineral density (BMD) in women with low bone mass: lumbar spine BMD in the exercise group (n=49) increased 2.9% [2.1% to 3.6%] versus –1.2% change in control (n=52) [–1.9% to –0.4%] and femoral neck BMD increased 0.1% [–0.7% to 0.8%] versus –1.8% change in control [–2.5 to –1.0%]. The effects on BMD in Watson et al 2017 should be interpreted with caution as it was a multicomponent (resistance training+high impact) intervention (i.e., not only back extensor/posture/core exercise) and not all participants had hyperkyphosis. **Physical functioning:** There is very low certainty evidence that exercises that target posture, back extensors or core stability can result in small improvements in physical functioning, measured using the Timed Up and Go test (MD 0.28 sec lower, 95% CI 0.48 lower to 0.08 lower, 4 RCTs 260 participants). Participants at baseline had an average score ranging from 7 to 16.4 seconds, and the mean difference may not be clinically significant. A sensitivity analysis in individuals with hyperkyphosis and either low bone mass or vertebral fractures at baseline demonstrates similar findings for Timed Up and Go performance (MD -2.7 seconds, -3.6 to -1.9, 2 studies, n=31, very low certainty evidence). The mean difference may be clinically important, although data on the minimal clinically important difference in this population is not available. The TUG test minimal clinically important difference ranges from 1.4 to 3.4 seconds in other populations with chronic musculoskeletal conditions. Another study reported no change in other physical functioning tests, such as the gait speed test and the 6 minute walk test in people with hyperkyphosis (Katzman et al, 2017 and 2017a). **Thoracic Spine Curvature:** There is high certainty evidence that exercise interventions that target back extensor muscles, core stability or posture in individuals with hyperkyphosis can improve spinal curvature to a small extent	Watson et al, 2018) used multicomponent interventions, not just back extensor muscle, core or posture exercises. The largest effects on spinal curvature were observed in a study by Katzman et al, 2017, which had a strong focus on back extensor strengthening, and targeted individuals with hyperkyphosis at baseline.

(SMD -0.22, -0.37 to -0.07, 8 RCTs n=679). The effect was not statistically significant when the analysis is restricted to individuals with low bone mass or vertebral fractures at baseline (SMD -0.07, 95% CI -0.26, 0.11, 5 RCTs, n=459).
Back extensor strength: There is very low certainty evidence (because of imprecision and risk of bias) that exercises targeting back extensor muscles, core stability or posture can improve back extensor strength compared to control (MD 10.51 N, 95%CI 6.61 to 14.38 N, 3 RCTs, n = 78). The change represents a 15-29% improvement over baseline values.
Back extensor endurance: Exercise improved back extensor muscle endurance assessed with the Timed Loaded Standing test (MD 9.76 sec, 95% CI 6.40, 13.13, 5 studies, 597 participants, low certainty evidence). Sensitivity analysis including only studies performed among people with both hyperkyphosis and low bone mass or vertebral fractures showed a significant mean difference in back extensor endurance in favour of exercise (MD 29.81 sec, 95% CI 22.61 to 37.01, 397 participants, 3 studies, low certainty evidence). The minimal clinically important difference for the Timed Loaded Standing test is not known; Shipp et al, 2000 reported that when looking at the average of two trials, the difference in group means between people with and without vertebral fractures was 43 seconds.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with No intervention	Risk difference with exercises targeting back extensor muscles, core stability or posture
Quality of Life assessed with: QUALEFFO-41 (score presented as higher score is better) follow up: range 6 weeks to 8 months	613 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	-		SMD **0.26 SD higher** (0.1 higher to 0.42 higher)
Physical functioning assessed with: Time Up and Go test (seconds, lower score is better) follow up: range 6 weeks to 3 months	260 (4 RCTs)	⨁◯◯◯ VERY LOW[a,b]	-	The mean physical functioning ranged from **7.0-16.4** seconds	MD **0.28 seconds lower** (0.48 lower to 0.08 lower)
Rate of falls assessed with: Total number of falls	537 (3 RCTs)	⨁⨁◯◯ LOW[b,c]	**Rate ratio 1.15** (0.64 to 2.05)	Study population	
				76 per 1,000	**11 more per 1,000** (27 fewer to 80

follow up: range 3 months to 6 months					more)
Fall-related injuries follow up: mean 3 months	348 (1 RCT)	⨁⨁◯◯ LOW[b]	-	One study reported 2 fall-related injuries in the intervention group (175 participants) and 3 fall-related injuries in the control group (173 participants).	
Fragility fractures follow up: mean 3 months	348 (1 RCT)	⨁⨁◯◯ LOW[b]	-	The number of events was too low to make inferences.	
Mortality follow up: mean 3 months	348 (1 RCT)	⨁⨁◯◯ LOW[b]	-	One study reported two deaths in the intervention group (170 participants) unrelated to intervention.	
Back extensor strength assessed with: Newton (higher score is better) follow up: range 4 months to 6 months	150 (3 RCTs)	⨁◯◯◯ VERY LOW[b,d]	-	The mean back extensor strength ranged from **34.75-65.41** Newtons	MD **10.51 Newtons higher** (6.65 higher to 14.38 higher)
Kyphosis curve assessed with: angle of index (lower is better) follow up: range 6 weeks to 8 months	679 (8 RCTs)	⨁⨁⨁⨁ HIGH	-		SMD **0.23 SD lower** (0.38 lower to 0.08 lower)

a. Serious unexplained heterogeneity
b. Low number of studies and/or participants
c. Confidence intervals overlap with the no difference line.
d. Outcome assessors were not blinded in one study and two studies have incomplete and selective outcome reporting.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	We updated an existing systematic review (Bansal et al, 2014) done by our team exploring the effects of exercise on hyperkyphosis. Our judgement was based on the available adverse event reporting in 5 trials, summarized in our systematic review (Ponzano et al, 2020). Of the 10 RCTs included, only five studies included information on adverse events (AEs) (5 RCTs, n=707). There were few undesirable events, but some studies did not report them, or did not report systematic methods to evaluate or verify them. **Undesirable effects:** Exercises for posture or back extensors does not increase the risk of serious adverse events in individuals with hyperkyphosis (including individuals with vertebral fractures), and although pain or musculoskeletal injuries are not uncommon when starting an exercise program, they were reported in both intervention and control groups (low certainty evidence due to risk of bias and imprecision). **Serious Adverse Events:** 5 RCTs reported on serious adverse events, none were reported. **Non-serious (or minor) Adverse Events:** 5 RCTs reported on minor adverse events. There was no statistically significant difference in minor adverse events between groups (IRR 1.29, 0.95 to 1.74, 5 studies, n=707, low certainty evidence). Only one study reported events attributable to intervention. Bennell et al 2010 reported that one control participant required physiotherapy because of back pain, and there were 6 minor AEs (11 participants) in intervention group related to intervention: shoulder pain (n = 2), flare-up of a wrist injury (n = 1), sore knee (n = 1) and a sore waist (n = 1) with certain exercises as well as irritation with the tape (n = 1). All resolved with intervention modification. Alin et al 2015 reported 12 minor AEs (38 participants) in intervention group vs 25 (37 participants) in the control group. One vertebral fracture occurred in the control group while cleaning house, and both groups reported muscle or joint complaints at a similar rate (4 intervention, 3 control). Barker et al 2019 reported 26 adverse events (including 5 falls and 6 fragility fractures) in the exercise group (216 participants) compared to 22 adverse events (including 4 falls and 8 fragility fractures) in 196 participants of the control group, but they do not state that any were attributable to the intervention. Katzman et al 2017 reported 30 minor Aes (51 participants) in intervention group vs 12 (48 participants) in the control group, but none were attributed to study participation. Katzman et al 2017a reported 56 adverse events (including 4 falls) in 53 participants of the intervention group and 31 adverse events (of which 7 were falls) during the 3-month waitlist period (48 participants); however, the majority of the musculoskeletal complaints were pre-existing and none of the events was attributable to the intervention.	

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with back extensor exercises
Serious adverse events follow up: range 3 months to 12 months	220 (5 RCTs)	⨁⨁◯◯ LOW[a]	-	No serious adverse events occurred during the interventions (n=707).	
Minor adverse events follow up: range 2.5 months to 12 months	707 (5 RCTs)	⨁⨁◯◯ LOW[a,b]	**Rate ratio 1.29** (0.95 to 1.74)	Study population	
				216 per 1,000	**63 more per 1,000** (11 fewer to 160 more)

a. Low number of studies and/or participants
b. Many studies did not report adverse events

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty was judged to be low. Although there is high certainty evidence that spinal curvature can be improved (which is the most relevant outcome targeted with the intervention in question), the evidence pertaining to harms is of low certainty. There is moderate certainty of evidence regarding effects on quality of life, and low or very low certainty of evidence regarding effects on falls, fractures, physical functioning or back extensor strength or endurance.	Patients would place a high value on effects on spinal curvature and quality of life.

Outcomes	Importance	Certainty of the evidence (GRADE)
Quality of Life assessed with: QUALEFFO-41 (score presented as higher score is better) follow up: range 6 weeks to 8 months		⨁⨁⨁◯ MODERATE[a]
Physical functioning assessed with: Time Up and Go test (seconds, lower score is better) follow up: range 6 weeks to 3 months		⨁◯◯◯ VERY LOW[a,b]
Rate of falls assessed with: Total number of falls follow up: range 3 months to 6 months		⨁⨁◯◯ LOW[b,c]
Fall-related injuries follow up: mean 3 months		⨁⨁◯◯ LOW[b]
Fragility fractures follow up: mean 3 months		⨁⨁◯◯ LOW[b]
Mortality follow up: mean 3 months		⨁⨁◯◯ LOW[b]
Serious adverse events follow up: range 3 months to 12 months		⨁⨁◯◯ LOW[b]
Minor adverse events follow up: range 2.5 months to 12 months		⨁⨁◯◯ LOW[b,d]
Back extensor strength assessed with: Newton (higher score is better) follow up: range 4 months to 6 months		⨁◯◯◯ VERY LOW[b,e]
Kyphosis curve assessed with: angle of index (lower is better) follow up: range 6 weeks to 8 months		⨁⨁⨁⨁ HIGH

a. Serious unexplained heterogeneity
b. Low number of studies and/or participants
c. Confidence intervals overlap with the no difference line.
d. Many studies did not report adverse events
e. Outcome assessors were not blinded in one study and two studies have incomplete and selective outcome reporting.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The following outcomes (in no particular order) were selected as a priority by >75% of respondents to a survey of 1108 members of the Canadian Osteoporosis Patient Network (96% were women; 86% were people living with OP, and the remaining 14% included caregivers and fitness instructors), listed in no particular order: Preserving quality of life and well-being. Preventing fracture related death Preventing admission to long-term care Preserving ability to perform daily activities Preventing all fractures related to osteoporosis Avoiding serious side-effects from drugs A survey in exercise professionals revealed similar priorities (in no particular order). Our working group of researchers, clinicians and a patient advocate used this information to identify the following outcomes as critical when making decisions about exercise: - mortality and fracture-related mortality - hip fractures and other fragility fractures - function and disability - quality of life - fall related injuries (or falls) - the potential for serious harm Non-serious adverse events were identified as important, but not critical outcomes. Bone mineral density was considered an indirect outcome related to hip or other fragility fractures when data on fractures were not available, but it was not a critical or important outcome on its own.	We believe we have captured the main outcomes that people value. However, patients may value the desirable and undesirable effects differently, and their values may change over time, or as their circumstances change. For example, people who have hyperkyphosis, or are concerned about it may value the potential benefits of this type of exercise more than individuals who do not have hyperkyphosis or are not worried about it. The majority of patients would likely place a high value on potential benefits and accept a potential small increase in risk of minor adverse events. Some people may overlook a lack of information on harms if there is a small potential for benefit. There may be a proportion of patients who might not be willing or able to accept potential risks e.g., low physical capacity, social/emotional barriers, high fall or fracture risk. People who are fearful of fractures, falls or adverse events may be concerned if information about risks is uncertain.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The undesirable effects are trivial, even in trials of individuals with vertebral fractures, although the evidence is of low certainty, and adverse events are not consistently reported. There are small but important benefits. The balance is weighed towards the benefits.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Participating in exercises targeting back extensor muscles, core stability or posture may require formal instruction, particularly in someone at risk of fracture. However, it may be possible to initiate independently using online resources or books. Therefore, there may be a cost, or concerns with access which could create health inequity; the costs may be greater for those at high risk of fracture, those with low exercise self-efficacy, those who fear falls or fractures, or who may not feel comfortable with an unsupervised approach. Patients may require instruction to understand what back extensor muscles are and how to target them, or target muscles important for posture or core stability.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	15 RCTs examined interventions that included back extensor strengthening, and adherence was reported in 10 of them, although the metrics used to report on adherence varied widely. In the RCTs, four studies reported adherence as % of participants who completed all or most sessions, and it ranged from 38% to 100% (median 75.5%). Six RCTs reported adherence as % of sessions completed and it ranged from 70.3% to 100% (median 84.5%). In a survey of members of the Canadian Osteoporosis Patient Network (COPN), 45% indicated that effects on posture was important to them when choosing to participate in exercise (Morin et al, 2020). However, a large majority of participants in RCTs and the COPN survey were women, and we do not have information on their socioeconomic status or other intersectional categories, thus, acceptability may be limited to women knowledgeable about osteoporosis and engaged in self-care.	Many of the studies involved fully or intermittently supervised interventions. The time commitment and cost required to participate in structured programs may be barriers. The level of instruction and support may influence acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	<u>Cost-effectiveness data in people with vertebral fractures</u> A study by Barker et al revealed that for people with symptomatic vertebral fractures, seven sessions with a physical therapist to get advice on home exercise was not more cost-effective than a single one-hour session with a physical therapist, and interventions that lead to improved adherence to physical therapy are needed. However, the intervention involved visits with a physical therapist to teach exercises that were to be done at home. It may be necessary to incorporate reminders or intermittent coaching for longer periods. Also, the intervention was not solely focused on treating hyperkyphosis. A small pilot study explored the feasibility of online approach to teaching exercises for back extensor muscles, core stability and posture, and the results were promising: improvements in spinal curvature, physical activity levels, and good adherence (Katzman et al 2019).	Experience with or knowledge of exercises for back extensor muscles or abdominal muscles, as well as socioeconomic status, baseline risk of fracture and comorbid conditions may influence the feasibility of implementing exercises for back extensor muscles, core stability or posture. The costs of this type of exercise depend on the level of need for equipment or instruction. The cost of ~5 sessions with a physical therapist or exercise physiologist is ~$400. It may be more accessible or cost less to attend a class led by other types of exercise professionals or attending small group personal training or learning from reputable online resources or instructors. Individuals at risk of fracture should consult exercise professionals with training on how to prescribe exercise for people with osteoporosis. The feasibility to implement it may vary based on access to exercise professionals (e.g., in less populated cities or towns, or rural areas).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest progressive resistance training ≥ twice weekly, including exercises targeting abdominal and back extensor muscles (GRADE: conditional recommendation, low certainty evidence).

Remark: Resistance training involves exercises where major muscle groups (e.g., upper and lower extremities, chest, shoulders, back) work against resistance (e.g, squats, lunges, and push-ups). Increase volume (e.g., sets, reps, weight), frequency, or difficulty to achieve progressive overload. Many resistance training exercises would be considered functional exercises.

Good practice statement: Activities that involve rapid, repetitive, sustained, weighted, or end-range twisting or flexion of the spine may need to be modified, especially in individuals at high risk of fracture. When available, seek advice from exercise professionals who have training on osteoporosis for exercise selection, intensity and progression, and activity modification, especially after recent fracture or if at high risk of fracture. When not available, refer to Osteoporosis Canada resources.

Justification

Exercises for posture and core stability, including exercises targeting back extensor muscles may improve quality of life, physical functioning, back extensor strength or endurance, and spinal curvature (very low to high certainty evidence) in individuals with hyperkyphosis. Effects on quality of life and physical functioning are similar in people at risk of fracture, but effects on spinal curvature may not occur. Effects on mortality, falls and fractures are uncertain (low certainty evidence). Potential harms are trivial (low certainty evidence), although pain or musculoskeletal injuries are not uncommon when starting an exercise program. Effects on physical functioning, quality of life and spinal curvature were important for decision-making. The certainty of evidence or size of effects were not sufficient to include a separate recommendation emphasizing this type of exercise for all people. Therefore, we recommend including it for people who are interested in improving posture or back extensor strength or endurance. Many of the interventions also included exercises for shoulder stabilizers, so those should also be considered in a strength or resistance training program.. While our literature review was focused on individuals with hyperkyphosis, several of the trials included individuals with low bone mass or vertebral fractures, suggesting that the findings related to effects on quality of life, physical functioning or back extensor strength and harms may be generalizable to these individuals.

Subgroup considerations

We suggest that the recommendation to participate in exercises targeting back extensor muscles and abdominal muscles, , applies to individuals with vertebral fractures or who are at high risk of fracture. Several of the trials included individuals with low bone mass or vertebral fractures, suggesting that the findings related to benefits and harms may be generalizable to these individuals. The positive effects of exercise on physical functioning and quality of life were observed in subgroup analyses limited to individuals with low bone mass or vertebral fractures at baseline. However, the ability of exercises for back extensor and abdominal muscles to improve thoracic curvature may vary depending on the factors contributing to hyperkyphosis (i.e., structural causes versus non-structural causes). In other words, one may be able to reduce hyperkyphosis due to restricted range of motion or weak back extensors, but vertebral fractures may cause a change in thoracic curvature that is not modifiable with exercise. Our analyses suggest that the effects of exercises targeting back extensor muscles, posture or core stability on spinal curvature were not statistically significant when limited to individuals with low bone mass or vertebral fractures.

Implementation considerations

Exercises targeting posture or abdominal and back extensor muscles can be delivered using a variety of modes (e.g., body weight exercises, resistance bands, machines), and can also be integrated into a progressive resistance training program for efficiency. Interventions in research studies involve having an exercise professional (e.g., clinical exercise physiologist, physical therapist) select exercises that will provide sufficient overload, provide coaching on alignment or technique and guide progression, in individual or group settings, and based on an assessment of an individual's capabilities. Guidance on exercise selection and proper form may affect the safety and efficacy of, and adherence to exercises for back extensors or core stability, particularly for individuals at high risk of fracture. All exercise programs should consider appropriate warm-up and cool-down activities, and consideration of breathing, alignment, and safety precautions.

Monitoring and evaluation

After implementation of the guidelines, it would be useful to evaluate:
- patients' and providers' understanding and acceptability of exercises for back extensor muscles, posture and core stability, and barriers to and facilitators of this type of exercise among individuals at risk of fracture
- the harms of exercises for back extensor muscles, posture and core stability
- the proportion of individuals at risk of fracture (and those at high risk) who participate in exercises targeting back extensor muscles, posture or core stability at the population level

Research priorities

· Do exercise programs that include exercises for back extensor and abdominal muscle and shoulder stabilizers , reduce fracture risk in individuals at risk of fractures (e.g., trials with fractures as primary outcome)?
· What are the harms of exercises for back extensor muscles, posture, and core stability in individuals over the age of 50 who are at increased risk of fracture?
· How can we effectively and equitably implement and scale up research on exercise for back extensor muscles, posture, and core stability in the real world? What is the cost-effectiveness of this type of training? What are the perspectives of people at risk of fracture on this type of training? Are there certain programs or types of exercise programs that are more acceptable to, or equitable or effective for patients (e.g., individual vs group or community-based programs, programs that incorporate back extensor training into things like yoga or Pilates)? Are there gender differences in the efficacy or the implementation of this type of training?

QUESTION 1: SHOULD CALCIUM SUPPLEMENTATION VERSUS NO SUPPLEMENTATION BE USED FOR INDIVIDUALS AT INCREASED RISK OF FRACTURE?

Should calcium supplementation vs. no supplementation be used for individuals at increased risk of fracture?	
POPULATION:	Individuals at increased risk of fracture
INTERVENTION:	calcium supplementation
COMPARISON:	no supplementation
MAIN OUTCOMES:	Fracture - Total fractures; Fracture - Hip; Fracture - Vertebral (Clinical); Fracture - Nonvertebral; BMD as surrogate measure; Falls; and adverse effects including Coronary Heart Disease, All-cause Mortality, Kidney Stones, Incident Cancer (nonskin), Myocardial Infarction, Stroke, Venous Thromboembolism, and Heart failure hospitalization.
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fractures are associated with significant morbidity and mortality among Canadians. Achieving the recommended dietary allowance (RDA) for calcium is important for bone health in healthy populations though many Canadians do not achieve the recommended level of intake for calcium (see additional considerations). Whether intake levels above the RDA through supplementation reduce the prevalence of fracture is of interest to clinicians, patients, and the general population. Moreover, the degree to which calcium intake levels are associated with fall risk, quality of life and adverse outcomes requires more investigation.	Many Canadians do not meet the current RDA for calcium which is 1200 mg for women over age 50 years, 1000 mg for men age 50-70 years and 1200 mg for age 70 years and older. **Percent of Canadian Women & Men with dietary Ca intakes at or above the RDA are the following:** ***Calcium from food alone*** Women: 51-70 years, 8%; >70 years, 5% Men: 51-70 years, 14%; >70 years, 10% ***Calcium from food + supplementation*** Women: 51-70 years, 35%; >70 years, 29% Men: 51-70 years, 22%; >70 years, 21% (Data from Vatanparast et al. Applied Physiology, Nutrition and Metabolism. 2009;34:191-196 using data from the Canadian Community Health Survey 2.2, Health Canada in 2004)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

With respect to desirable effects on fracture risk, there was moderate to high certainty evidence that calcium supplementation provides trivial benefits, whether it was hip, total or vertebral fracture. This finding was supported by high certainty BMD evidence at multiple sites (femur neck, vertebra, total body, forearm).

The following table reports effects of calcium supplementation in 1000 people over 1 year:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with calcium supplementation
Fracture - Hip (SR: Zhao et al. 2017)(risk per 1000 people over 1 year) follow up: range 2 years to 5 years	6703 (6 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 1.53** (0.97 to 2.42)	Study population	
				16 per 1,000	**9 more per 1,000** (0 fewer to 23 more)
				High	
				3 per 1,000	**2 more per 1,000** (0 fewer to 4 more)
Fracture - Total (SR: Zhao et al. 2017)(risk per 1000 people over 1 year) follow up: range 2 years to 5 years	6787 (7 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.88** (0.75 to 1.03)	Study population	
				141 per 1,000	**17 fewer per 1,000** (35 fewer to 4 more)
				High	
				30 per 1,000	**4 fewer per 1,000** (8 fewer to 1 more)
Fracture - Vertebral (SR: Zhao et al. 2017)(risk	6517 (9 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.83** (0.66 to 1.05)	Study population	
				42 per 1,000	**7 fewer per 1,000** (14 fewer to 2 more)
				High	

ADDITIONAL CONSIDERATIONS

For fracture outcomes, a subgroup analysis was done by Zhao et al. (JAMA 2017) for the following factors:
i. level of Ca supplementation, ≥ 1 or <1 g/d;
ii. trials that include only women versus women+men;
iii. previous fractures, yes or no;
iv. baseline Ca intake, ≥ 900 or < 900 mg/d; or
v. baseline serum 25OHD, ≥ 20 or < 20 ng/mL (or ≥ 50 or < 50 nmol/L).
This subgroup analysis showed the same findings as the full analysis *though the number of studies may be considered quite small within each subgroup analysis such that there is concern that baseline intakes of Ca or baseline status of vitamin D should perhaps be considered. The number of trials for each category is a n of 4 through 9.*

It is important to keep in mind that these studies within the SR by Zhao et al. 2017 have not included individuals receiving pharmacotherapy. Thus, the desirable effects of calcium supplementation may be different in a patient population at high risk of fracture and receiving pharmacotherapy.

per 1000 people over 1 year) follow up: range 2 years to 5 years				15 per 1,000	**3 fewer per 1,000** (5 fewer to 1 more)
BMD - Total Hip (SR: Tai et al. 2015) assessed with: DXA follow up: range 3 years to 5 years	6374 (6 RCTs)[b,c]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Total Hip (SR: Tai et al. 2015) was **0** %	MD **1.2 % higher** (0.5 higher to 1.9 higher)
BMD - Total Body (SR: Tai et al. 2015) assessed with: DXA follow up: mean 1 years	7594 (7 RCTs)[b,c]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Total Body (SR: Tai et al. 2015) was **0** %	MD **0.8 % higher** (0.5 higher to 1.1 higher)
BMD - Lumbar Spine (SR: Tai et al. 2015) assessed with: DXA follow up: range 3 years to 5 years	6622 (8 RCTs)[b,c]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Lumbar Spine (SR: Tai et al. 2015) was **0** %	MD **1 % higher** (0.3 higher to 1.6 higher)
BMD - Femoral Neck (SR: Tai et al. 2015) assessed with: DXA follow up: range 3 years to 5 years	3666 (5 RCTs)[b,c]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Femoral Neck (SR: Tai et al. 2015) was **0** %	MD **1.5 % higher** (0.2 higher to 2.9 higher)

BMD - Forearm (SR: Tai et al. 2015) assessed with: DXA follow up: mean 1 years	716 (5 RCTs)[b,c]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Forearm (SR: Tai et al. 2015) was **0** %	MD **1.8 % higher** (0.2 higher to 3.4 higher)
BMD - Lumbar (L2-L4)(SR: Wu et al. 2017) follow up: range 10 months to 2 years	0 (17 RCTs)	⨁⨁⨁⨁ HIGH[d]	-	This study describes the observed time-course of spine BMD (L2-L4) change by calcium intake using a classic pharmacodynamic model in postmenopausal women (17 trials, 2537 subjects). The mathematical model from the meta analysis suggests that a 60 year old woman administered with 800 mg/d of calcium can achieve a maximum increase in BMD (~2.28%) with time to reach 50% of this maximum (i.e., onset time) at 9.44 months. Interpretation of the model demonstrates that a dose of 1200 mg/d for 2 yrs would be sufficient to reach the efficacy plateau for this treatment. The authors conclude that calcium intake can effectively postpone the tendency of BMD decrease in postmenopausal women, that increased calcium dose contributes to the shortening of the onset time, and suggest an a rational dose of 1200 mg/d to reduce bone loss.		

a. Insufficient number of cases or participants to avoid risk of bias in recommendation of the intervention
b. Data reported from Tai et al. (2015) included trials >2.5 years; however, see manuscript for data after 1 and 2 years of treatment
c. No clear risk or change in BMD (mean difference, %) reported for 'Control/Placebo' during the trial
d. The meta analysis by Wu et al. (2017) does not directly assess the risk/benefit of Calcium supplementation vs. no supplementation, nor does it provide a comprehensive dose-response relationship.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

The reported undesirable effects of calcium supplementation were trivial.

The following table reports effects of calcium supplementation in 1000 people over 1 year:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with calcium supplementation
Adverse - Kidney Stones (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: range 2 years to 4 years	1259 (3 RCTs)	⨁⨁⨁◯ MODERATE[a,b]	**RR 0.68** (0.14 to 3.36)	Study population	
				6 per 1,000	**2 fewer per 1,000** (5 fewer to 14 more)
				Low	
				10 per 1,000	**3 fewer per 1,000** (9 fewer to 24 more)
Adverse - Coronary Heart Disease (SR: Lewis et al. 2015)(risk per 1000 people over 1 year) follow up: range 1 years to 5.2 years	48460 (6 RCTs)[c]	⨁⨁⨁⨁ HIGH	**RR 1.02** (0.96 to 1.09)	Study population	
				69 per 1,000	**1 more per 1,000** (3 fewer to 6 more)
				Low	
				60 per 1,000	**1 more per 1,000** (2 fewer to 5 more)
Adverse - Incident Cancer (nonskin)(SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: mean 4 years	733 (1 RCT)	⨁⨁◯◯ LOW[a,d]	**RR 0.55** (0.29 to 1.03)	Study population	
				69 per 1,000	**31 fewer per 1,000** (49 fewer to 2 more)
				Low	
				50 per 1,000	**23 fewer per 1,000** (36 fewer to 2 more)
Adverse - Myocardial Infarction (SR: Kahwati et al. 2018)(risk per 1000 people over	290 (1 RCT)	⨁◯◯◯ VERY LOW[a,d,e]	**RR 3.03** (0.12 to 73.49)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Low	

1 year) follow up: range 4 months to 7 years				25 per 1,000	**51 more per 1,000** (22 fewer to 1,812 more)	

a. Insufficient number of cases or participants to avoid risk of bias in recommendation of the intervention
b. Insufficient number of events to ensure precision and adequate power
c. Of the studies included in this analysis, one included individuals who consumed Vitamin D supplements
d. Only one RCT included and not sufficiently powered to assess this outcome
e. Included predominantly white men (>40yrs) in New Zealand, doses 600-1200mg/day

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Certainty of fracture and BMD data is moderate to high. For adverse effects, certainty was varied by specific outcomes and ranged from very low to high, but did not indicate harm or benefit.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The main outcomes were decided upon based on results of the Canadian Osteoporosis Patient Network (COPN) survey as well as the perspectives of the diet working group members which included a patient member, a general physician and academic researchers. The main outcomes included the following: -Fracture (and BMD at various skeletal sites was also considered, particularly whether BMD aligned with or was supportive of fracture data) -Falls -Adverse Effects -Quality of Life There was no important uncertainty about or variability in how much people value the main outcomes. Patients identified fracture reduction as an important main outcome.	Results of the Canadian Osteoporosis Patient Network (COPN) survey have been published: Morin et al. Osteoporosis International. 2020;31(5):867-874. Figure 1 from this paper lists outcomes critical to consider in osteoporosis management guideline development. Of note is that this list includes preserving quality of life, preventing fracture and avoiding serious side effects from drugs (and possibly supplement use). Reducing falls would be associated with preventing fractures. Each of these was ranked similarly high by respondents. The majority of respondents were patients.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The desirable effects are likely trivial and the undesirable effects of calcium supplementation may be trivial. There was no data on the effect of calcium supplementation on falls or quality of life.	Intakes of calcium among individuals within studies and between studies can be highly variable and thus are above or below the RDA for calcium. Though, data suggest that dietary calcium intakes of Canadians are not consistently at the RDA such that supplementation may help some individuals reach appropriate baseline status. Desirable effects of calcium supplementation may be attenuated in individuals with sufficient baseline status (sufficient baseline status is defined as meeting the RDA for calcium).

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Calcium supplementation is relatively inexpensive. A calcium supplement (specifically calcium carbonate) containing **500 mg of calcium would cost approximately $0.05 per pill.** An individual may choose to 'supplement' with calcium using foods. One serving of milk (250 mL) provides approximately **300 mg of dietary calcium and costs $0.27 per serving** ($4.39/4 L of skim, 1% or 2% milk). For those who choose not to or cannot consume dairy, several beverages such as orange juice or soy or almond beverages are fortified with calcium, at approximately the level present in milk (300 mg calcium per serving). Costs are the following: Calcium fortified orange juice: **$0.35 per 250 mL serving** ($2.78/2 L) Calcium fortified soy or almond beverage: **$0.50 per 250 mL serving** ($3.98/2 L)	Calcium supplements are less expensive than food sources of calcium that contain the largest amounts of calcium per serving. These foods include cow's milk as well as foods fortified with calcium such as orange juice or plant-based beverages. There is no strong evidence that there are differences in bioavailability due to source (supplement, food source) in terms of benefits to bone health.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ● High ○ No included studies	There is high certainty regarding the cost of calcium supplements or obtaining additional calcium through a food source.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		Although the cost of increasing the intake of calcium through supplementation or diet is inexpensive, it is an additional cost for trivial benefits and harms.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Given the low cost of calcium supplements and that calcium can be obtained through food sources relatively inexpensively, there would likely be no impact on health equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The use of calcium supplements is acceptable by key stakeholders including patients and health care providers. Also, calcium supplements are recommended within long term care guidelines for prevention of fracture (Papaioannou et al. Canadian Medical Association Journal. 2015;187(15);1135-1144. Recommendations for preventing fracture in long-term care).	Results of the Canadian Osteoporosis Patient Network (COPN) survey identified interest in understanding how calcium, vitamin D and other nutrients - including vitamin K and protein - can benefit bone health (Morin et al. Osteoporosis International. 2020;31(5):867-874).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Many different forms of calcium supplements have been studied but the majority of studies have used calcium carbonate. In the review by Zhao et al. 2017, the following forms of calcium supplements were represented within individual studies: calcium carbonate (n=14 trials); calcium lactate (n=3 trials); calcium citrate malate (n=2 trials); combination of bicarbonate, lactate and gluconate (n=1 trial); combination of lactate, gluconate and carbonate (n=1 trial), unreported in 1 trial. Calcium supplements are widely available and relatively inexpensive and thus are feasible to implement. Use of calcium supplementation has been a recommendation of previous clinical practice guidelines in Canada.	It is unlikely that form of calcium affects efficacy provided it is taken appropriately (i.e., calcium carbonate with meals to aid with absorption) Can also consider that antacid use can be a form of calcium supplement that is widely used and acceptable.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals meeting calcium recommended dietary allowances with a variety of calcium rich foods, we suggest no supplementation of calcium to prevent fractures.

Justification

Overall justification

Calcium supplementation was shown to provide only a trivial benefit in terms of reduction of fracture regardless of site (hip, total, vertebral) and this is based on evidence with moderate to high certainty. Undesirable effects were determined to be trivial though certainty of evidence ranged from very low to high for different outcomes. In addition to fracture prevention and concern about side-effects, there were no data about other main outcomes that are considered important by patients such as quality of life or fall prevention. Calcium supplementation is quite inexpensive and some individuals may choose to increase calcium intake through consumption of calcium rich foods such as milk or beverages that are fortified with calcium and at approximately the same level of calcium as is naturally present in milk.

Detailed justification

Desirable Effects

Emphasis was placed on fractures (hip, total, nonvertebral and vertebral). Moreover, BMD at multiple sites (femur neck, vertebra, total body, forearm) was aligned with the findings regarding a trivial effect of calcium supplementation on fracture.

Subgroup considerations

Implementation considerations

Use of supplements is generally acceptable to Canadians and requires no special implementation considerations. However, more careful consideration may be required for some individuals when dietary supplements are taken with other medications in terms of route and timing of ingestion. Form of calcium supplementation can influence when/how it is taken. For example, calcium carbonate may be less expensive but needs to be taken with meals whereas calcium citrate can be taken at any time during the day, irrespective of the timing of a meal.

Monitoring and evaluation

Baseline dietary calcium intake can be quickly estimated by a patient and/or their health care provider. For example, one serving of dairy contains 300 mg of calcium and approximately 300 mg of calcium is consumed by eating a mixed diet as many foods contain small amounts of calcium. There is an upper tolerable level (UL) for calcium of 2000 mg per day for both men and women over age 50 years. Intakes beyond 2000 mg per day have no known benefit to health, including bone health, and can lead to potential adverse effects. Thus, supplements should only be used to help assist an individual meet the dietary recommended intake after estimating calcium intake through food sources.

Research priorities

Though it would be ideal to have RCTs in individuals at high risk of fracture, this is unrealistic as it would be unethical to with-hold pharmacotherapy and those individuals who choose not to take pharmacotherapy may differ in multiple ways from 'general population' and thus attenuate applicability of findings to the general population.

Potential research areas:
Response to calcium supplementation in terms of how long it takes to change calcium status to impact bone health
Equivalency of food versus supplemental source on calcium status

QUESTION 2: SHOULD VITAMIN D SUPPLEMENTATION VERSUS NO SUPPLEMENTATION BE USED FOR INDIVIDUALS AT INCREASED RISK OF FRACTURE?

Should vitamin D supplementation vs. no supplementation be used for individuals at increased risk of fracture?	
POPULATION:	Individuals at increased risk of fracture
INTERVENTION:	vitamin D supplementation
COMPARISON:	no supplementation
MAIN OUTCOMES:	Fracture - Total fractures; Fracture - Hip; Fracture - Vertebral (Clinical); Fracture - Nonvertebral; BMD as surrogate measure; Falls; and adverse effects including Coronary Heart Disease, All-cause Mortality, Kidney Stones, Incident Cancer (nonskin), Myocardial Infarction, Stroke, Venous Thromboembolism, and Heart failure hospitalization.
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fractures are associated with significant morbidity and mortality among Canadians. Achieving the dietary reference intake RDA for vitamin D is important for bone health in healthy populations. Whether intake levels above the RDA through supplementation reduce the prevalence of fracture is of interest to clinicians, patients, and the general population. Moreover, the degree to which vitamin D intake levels are associated with fall risk, quality of life and adverse outcomes requires more investigation.	Canadian data suggests that some Canadian men and women are not meeting the target serum 25OHD levels of ≥ 50 nmol/L **Percent of Women & Men with serum 25OHD below 30 or 40 nmol/L:** **<30 nmol/L** Women: 51-70 years, 6%; 71-79 years, 3% Men: 51-70 years, 8%; 71-79 years, 5% **<40 nmol/L** Women: 51-70 years, 14%; 71-79 years, 10% Men: 51-70 years, 19%; 71-79 years, 14%

		(data from Canadian Health Measures Survey, Cycles 1 to 3, as reported by Brooks S et al. Journal of AOAC International 2017;100(5):1345-1354) **Vitamin D Status Cut-Points used by the Institute of Medicine (IOM) and Health Canada (serum 25OHD levels):** <30 nmol/L - high risk of vitamin D deficiency 30 to <50 nmol/L - potential risk of inadequacy in terms of bone health ≥50 nmol/L - generally considered adequate for bone and overall health in healthy individuals >125 nmol/L - linked to potential adverse effects

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

There was no desirable effect of vitamin D supplementation on fracture risk evident in the high certainty data we have reported, whether it was hip, total or vertebral. This finding was supported by BMD evidence at multiple sites (total hip, total body, lumbar spine, femoral neck, forearm). With respect to falls, there was also a trivial decrease.

This table reports results of the effects of vitamin D supplementation in 1000 persons over 1 year:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with vitamin D supplementation
Fracture - Hip (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858)(risk per 1000 people over 1 year)	36370 (17 RCTs)[a]	⨁⨁⨁⨁ HIGH	**RR 1.12** (0.98 to 1.28)	Study population	
				22 per 1,000	**3 more per 1,000** (0 fewer to 6 more)
				High	
				3 per 1,000	**0 fewer per 1,000** (0 fewer to 1 more)
Fracture - Total (SR: Bolland et al. 2018, Lancet Diabetes	39485 (24 RCTs)[a]	⨁⨁⨁⨁ HIGH	**RR 1.01** (0.94 to 1.10)	Study population	
				84 per 1,000	**1 more per 1,000** (5 fewer to 8 more)

ADDITIONAL CONSIDERATIONS

For fracture, BMD and falls, subgroup analyses were performed using the following factors:
i. age, <65 years of age versus ≥65 years of age
ii. BMI, <30 vs ≥30 kg/m2
iii. baseline 25OHD, <25 nmol/L vs ≥25 nmol/L, <50 nmol/L vs ≥50 nmol/L, <75 nmol/L vs ≥75 nmol/L; or
iv. achieved 25OHD, <50 nmol/L vs ≥50 nmol/L, <75 nmol/L vs ≥75 nmol/L
The subgroup analyses showed the same findings as the full analysis - suggesting that findings are applicable to individuals that may differ according to age, BMI, baseline vitamin D status or achieved vitamin D status. Findings are that vitamin D supplementation does not prevent fractures or falls or have clinically meaningful effects on BMD.
(Bolland et al. Lancet Diabetes Endocrinol, 2018;6(11):847-858. See p. 28 of supplementary appendix)

It is important to keep in mind that these studies within these SRs have not included individuals receiving pharmacotherapy. Thus, the desirable effects of Vit D supplementation may be different in a patient population at high risk of fracture and receiving pharmacotherapy.

Endocrinol 2018;6(11):847-858)(risk per 1000 people over 1 year)				High		
				30 per 1,000	**0 fewer per 1,000** (2 fewer to 3 more)	
Fracture - Vertebral (SR: Zhao et al. 2017)(risk per 1000 people over 1 year) follow up: range 2 years to 5 years	7689 (4 RCTs)	⨁⨁⨁⨁ HIGH[b]	**RR 0.97** (0.54 to 1.77)	Study population		
				15 per 1,000	**0 fewer per 1,000** (7 fewer to 12 more)	
				High		
				15 per 1,000	**0 fewer per 1,000** (7 fewer to 12 more)	
BMD - Total Hip (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858)(final timepoint reported in each RCT) assessed with: DXA	5348 (29 RCTs)[a]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Total Hip (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858)(final timepoint reported in each RCT) was **0** %		MD **0.34 % higher** (0.13 higher to 0.55 higher)
BMD - Total Body (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858) assessed with: DXA	3143 (16 RCTs)[a]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Total Body (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858) was **0** %		MD **0.13 % higher** (0.16 lower to 0.42 higher)
BMD - Lumbar Spine (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858)(final timepoint value reported in each	6038 (34 RCTs)[a]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Lumbar Spine (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858)(final timepoint value reported in each RCT) was **0** %		MD **0.25 % higher** (0 to 0.49 higher)

RCT) assessed with: DXA					
BMD - Femoral Neck (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858) assessed with: DXA	5187 (28 RCTs)[a]	⨁⨁⨁⨁ HIGH	-	The mean BMD - Femoral Neck (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858) was **0** %	MD **0.76 % higher** (0.42 higher to 1.09 higher)
BMD - Forearm (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858) assessed with: DXA	1667 (11 RCTs)[a]	⨁⨁⨁◯ MODERATE[b]	-	The mean BMD - Forearm (SR: Bolland et al. 2018, Lancet Diabetes Endocrinol 2018;6(11):847-858) was **0** %	MD **0.16 % lower** (0.46 lower to 0.13 higher)
Falls (SR: Bolland et al. 2018)(risk per 1000 people over 1 year)	26642 (26 RCTs)[a]	⨁⨁⨁⨁ HIGH	**RR 0.97** (0.93 to 1.02)	Study population	
				495 per 1,000	**15 fewer per 1,000** (35 fewer to 10 more)
				High	
				20 per 1,000	**1 fewer per 1,000** (1 fewer to 0 fewer)

a. The majority of studies included in Bolland et al. 2018 studied community dwelling individuals (mostly female), although individuals at high risk for fracture were not specifically targeted.
b. Insufficient number of cases or participants to avoid risk of bias in recommendation of the intervention

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

The available moderate quality evidence describing undesirable effects of vitamin D supplementation on incident cancer, myocardial infarction, and cerebrovascular disease were trivial.

This table reports results of the effects of vitamin D supplementation in 1000 persons over 1 year:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with vitamin D supplementation
Adverse - Incident Cancer (non-skin)(SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: mean 5 years	2918 (2 RCTs)	⨁⨁⨁◯ MODERATE[a,b]	**RR 1.08** (0.89 to 1.30)	Study population	
				121 per 1,000	**10 more per 1,000** (13 fewer to 36 more)
				Low	
				50 per 1,000	**4 more per 1,000** (6 fewer to 15 more)
Adverse - Myocardial Infarction (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: range 2.5 years to 4.2 years	5108 (1 RCT)[c]	⨁⨁⨁◯ MODERATE[b,d,e]	**HR 0.90** (0.54 to 1.50)	Study population	
				64 per 1,000	**6 fewer per 1,000** (29 fewer to 30 more)
				Low	
				25 per 1,000	**2 fewer per 1,000** (11 fewer to 12 more)
Adverse - Cerebrovascular Disease / Stroke (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: range 2.5 years to 4.2	5108 (1 RCT)[c]	⨁⨁⨁◯ MODERATE[b,d]	**HR 0.95** (0.55 to 1.62)	Study population	
				12 per 1,000	**1 fewer per 1,000** (5 fewer to 7 more)
				Low	
				30 per 1,000	**1 fewer per 1,000** (13 fewer to 18

ADDITIONAL CONSIDERATIONS

years					more)	

a. High level of variability between the two RCTs included in this analysis
b. Meta-analysis by Kahwati et al. (2018) excluded participants that would be classified as high risk for fracture. "Excluded if participant enrollment was based on known high risk of fracture or falls or if more than 20% of participants had a prior history of Osteoporotic fractures or prevalent fractures at baseline".
c. RCT evidence sourced from Kahwati et al. 2018 (VIDA Study, Scragg et al. 2017), the only study for this outcome that was sufficiently powered for cardiovascular disease events.
d. Studies underpowered for this outcome; not enough evidence to ascertain the influence of dose, route or frequency on incidence
e. Insufficient number of cases or participants to avoid risk of bias in recommendation of the intervention

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Certainty of fracture and BMD data and falls is moderate to high. For adverse effects, certainty was moderate.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes were decided upon based on results of the Canadian Osteoporosis Patient Network (COPN) survey as well as the perspectives of the diet working group members which included a patient member, a general physician and academic researchers. The outcomes included the following: -Fracture (and BMD at various skeletal sites was also considered, whether BMD was aligned with/supportive of fracture data) -Falls -Adverse Effects	Results of the Canadian Osteoporosis Patient Network (COPN) survey have been published: Morin et al. Osteoporosis International. 2020;31(5):867-874. Figure 1 from this paper lists outcomes critical to consider in osteoporosis management guideline development. Of note is that this list includes preserving quality of life, preventing fracture and avoiding serious side effects from drugs (reducing

	-Quality of Life Because falls are a major cause of fracture and patients identified fracture reduction as an important main outcome there is proabbly no important uncertainty or variability in how much people value this main outcome.	falls would be associated with preventing fractures). Each of these was ranked similarly high by respondents. The majority of respondents were patients.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Based on the moderate certainty evidence the balance of the trivial benefits and harms does not favour vitamin D supplementation.	Baseline serum 25OHD (and achieved serum 25OHD) among individuals within studies and between studies can be highly variable and thus may be below (<50 nmol/L) sufficient status. While it may seem that desirable effects of vitamin D supplementation may be attenuated in individuals with sufficient baseline status (defined as serum 25OHD >50 nmol/L), subanalysis by baseline serum 25OHD status resulted in similar results as the full analysis. (Bolland et al. 2018). Canadian data suggests that vitamin D intakes are not at the recommended level for all, such that supplementation may help some individuals reach appropriate baseline status.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Vitamin D supplementation is relatively inexpensive. A vitamin D supplement containing **1000 IU of vitamin D in the form of 'drops' is $0.10 per drop.** An individual may choose to 'supplement' with vitamin D using foods. One serving of milk (250 mL) provides approximately **100 IU vitamin D and costs $0.27 per serving** ($4.39/4 L of skim, 1% or 2% milk). For those who choose not to or cannot consume dairy, several beverages such as orange juice or soy or almond beverages are fortified with vitamin D. The level of vitamin D is lower than that in cow's milk, at approximately 50 IU per serving in orange juice or 85 IU per serving in soy or almond beverage. Costs are the following: Vitamin D fortified orange juice: **$0.35 per 250 mL serving** ($2.78/2 L) Vitamin D fortified soy or almond beverage: **$0.50 per 250 mL serving** ($3.98/2 L). Salmon would represent a food source of vitamin D for Canadians though cost varies as does the vitamin D level. Farmed fish contains much lower levels of vitamin D (approximately 250 IU/serving) compared to approximately 1000 IU per serving for wild salmon. Costs are variable from **$2.60 to $4.40 per 100 g serving for fresh or frozen**. **Canned salmon is less expensive at $2.10 per 100 g serving** and also contains calcium as the bones are softened and can be consumed.	Vitamin D supplements are less expensive than food sources of vitamin D that contain the highest amounts of these nutrients per serving. These foods include cow's milk as well as foods fortified with vitamin D such as orange juice or soy or almond beverages. There is no strong evidence that there are differences in bioavailability due to source in terms of benefits to bone health.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	There is high certainty regarding the cost of vitamin D supplements or obtaining additional vitamin D through a food source.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost-effectiveness probably favours the comparison. The cost of vitamin D supplements is inexpensive. Food sources may be less desirable for vitamin D due to naturally low levels in many foods. For example, commonly foods containing larger amounts of vitamin D such as salmon (>300 IU/serving) are not widely consumed by Canadians on a regular basis due to a variety of reasons including cost. Milk provides a relatively low level of vitamin D in terms of meeting the dietary recommended intake but it is among the foods sources that contains high amounts of vitamin D per serving (100 IU/serving).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Given the low cost of vitamin D supplements there would likely be no impact on health equity. If using food sources to increase intake of vitamin D that would be challenging in terms of foods sources and the respective levels per serving and cost is also a consideration.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, the intervention is acceptable by key stakeholders including patients and health care providers. Also, vitamin D supplementation is widely used in Canadian population – somewhat due to current recommendations by clinicians and attention in the media about many different health benefits in bone and other tissues. Vitamin D has been part of previous recommendations regarding prevention of fracture. Also, vitamin D supplements are recommended within long term care guidelines for prevention of fracture (Papaioannou et al. CMAJ. 2015;187(15);1135-1144. Recommendations for preventing fracture in long-term care).	Results of the Canadian Osteoporosis Patient Network (COPN) survey identified interest in understanding how calcium, vitamin D and other nutrients - including vitamin K and protein - can benefit bone health (Morin et al. Osteoporosis International. 2020;31(5):867-874)

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Vitamin D supplements are widely available and relatively inexpensive, and have been implemented as part of the prevention and management of previous fracture guidelines.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals who are 50 years and older, we suggest no supplementation of vitamin D beyond Health Canada's recommendation of a 400 IU supplement/day, to prevent fractures (GRADE: conditional recommendation, high certainty evidence)

Justification

Supplementation with vitamin D shows trivial benefits in terms of reduction of fracture regardless of site (hip, total, vertebral) or reduction of falls and this is based on moderate to high certainty evidence. Undesirable effects were also trivial based on moderate certainty evidence. There were no data about quality of life, another main outcome of interest. Individuals with low baseline intakes of vitamin D would benefit from supplements to bring them to the recommended intakes (RDA) that have been established for overall bone health. Adequate intake/status of vitamin D, is important to support bone health. Supplementation with vitamin D is quite inexpensive. Some individuals may choose to increase vitamin D intake through consumption of foods that naturally contain vitamin D or are fortified with vitamin D.

Subgroup considerations

Implementation considerations

Use of vitamin D supplements is generally acceptable to Canadians and requires no special implementation considerations.

Monitoring and evaluation

There is an upper tolerable level (UL) for vitamin D of 4000 IU per day for both men and women over age 50 years. Intakes beyond 4000 IU vitamin D per day have no known benefit to health, including bone health, and can lead to potential adverse effects.

Research priorities

Though it would be ideal to have RCTs in individuals at high risk of fracture, this is unrealistic as it would be unethical to with-hold pharmacotherapy and those individuals who choose not to take pharmacotherapy may differ in multiple ways from ‘general population’ and thus attenuate applicability of findings to the general population. Must also consider the SR by Bolland et al. 2018 (Lancet Diabetes Endocrinol, 2018;6(11):847-858) in which a strong argument is made against future trials being needed as a 'no effect' of vitamin D supplementation for musculoskeletal health is conclusive based on existing studies.

Comprehensive dose-response curves may be useful.

Response to vitamin D supplementation, in terms of how long it takes to change vitamin D3 status – and in the context of differing BMI/obesity. In other words, combining multiple factors that may have not been captured together in the subgroup analyses in which single factors were considered.

QUESTION 3: SHOULD CALCIUM AND VITAMIN D SUPPLEMENTATION VERSUS NO SUPPLEMENTATION BE USED FOR INDIVIDUALS AT INCREASED RISK OF FRACTURE?

Should calcium and vitamin D supplementation vs. no supplementation be used for individuals at increased risk of fracture?	
POPULATION:	Individuals at increased risk of fracture
INTERVENTION:	calcium and vitamin D supplementation
COMPARISON:	no supplementation
MAIN OUTCOMES:	Fracture - Total fractures; Fracture - Hip; Fracture - Vertebral (Clinical); Fracture - Nonvertebral; BMD as surrogate measure; Falls; and adverse effects including Coronary Heart Disease, All-cause Mortality, Kidney Stones, Incident Cancer (nonskin), Myocardial Infarction, Stroke, Venous Thromboembolism, and Heart failure hospitalization.
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fractures are associated with significant morbidity and mortality among Canadians. The biological roles of calcium and vitamin D are inextricably linked with respect to supporting bone health – vitamin D regulates calcium metabolism at three critical sites: intestine, bone and kidney. Therefore, knowing how simultaneous supplementation with both nutrients modulates fracture and other outcomes is of particular interest. Moreover, calcium has an integral structural role in the formation of hydroxyapatite while vitamin D is increasingly understood to have functional role beyond the skeleton in other tissues (muscle is one example, vitamin D receptor (VDR) has been found in tissues throughout the body). Achieving the RDA for calcium and vitamin D is important for bone health in healthy populations. Whether intakes levels above the RDA through supplementation reduce the prevalence of fracture is of interest to clinicians, patients, and the general population. Moreover, the degree to which calcium and vitamin D intake levels are associated with fall risk, quality of life, and adverse outcomes requires more investigation.	**Calcium** Many Canadians do not meet the current RDA for calcium which is 1200 mg for women over age 50 years, 1000 mg for men age 50-70 years and 1200 mg for age 70 years and older. **Percent of Canadian Women & Men with dietary calcium intakes at or above the RDA are the following:** ***Calcium from food alone*** Women: 51-70 years, 8%; >70 years, 5% Men: 51-70 years, 14%; >70 years, 10% ***Calcium from food + supplementation*** Women: 51-70 years, 35%; >70 years, 29% Men: 51-70 years, 22%; >70 years, 21% (Vatanparast et al. Applied Physiology, Nutrition and Metabolism. 2009;34:191-196 using data from the Canadian

		Community Health Survey 2.2, Health Canada in 2004) **Vitamin D** Canadian data suggests that some Canadian men and women are not meeting the target serum 25OHD levels of ≥ 50 nmol/L **Percent of Women & Men with serum 25OHD below 30 or 40 nmol/L:** **<30 nmol/L** Women: 51-70 years, 6%; 71-79 years, 3% Men: 51-70 years, 8%; 71-79 years, 5% **<40 nmol/L** Women: 51-70 years, 14%; 71-79 years, 10% Men: 51-70 years, 19%; 71-79 years, 14% (data from Canadian Health Measures Survey, Cycles 1 to 3, as reported by Brooks S et al. Journal of AOAC International 2017;100(5):1345-1354) **Vitamin D Status Cut-Points used by the Institute of Medicine (IOM) and Health Canada (serum 25OHD levels):** <30 nmol/L - high risk of vitamin D deficiency 30 to <50 nmol/L - potential risk of inadequacy in terms of bone health ≥50 nmol/L - generally considered adequate for bone and overall health in healthy individuals >125 nmol/L - linked to potential adverse effects

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	There was high certainty evidence that any desirable effect of combined vitamin D and calcium supplementation on fracture risk was trivial, whether it was hip, total or vertebral fracture. This finding was supported by multi-site BMD evidence that there was no apparent desirable effect of i) vitamin D supplementation in individuals already consuming calcium, or ii) calcium supplemetation in individuals already consuming vitamin D. With respect to falls, there was a trivial decrease with vitamin D supplementation reported in comparison to control/placebo data (there was moderate certainty for the falls data).	**For fracture outcomes (hip & total), a subgroup analysis was done by Zhao et al. JAMA 2017 for the following factors:** i. Calcium and Vitamin D dose and frequency (≥1 g/d and ≥800 IU/d or "other") ii. trials that include only women versus women+men; iii. previous fractures, yes or no; iv. baseline calcium intake, ≥ 900 or < 900 mg/d; or v. baseline serum 25OHD, ≥ 20 or < 20 ng/mL (or ≥ 50 or < 50 nmol/L).

This table reports results of the effects of calcium + vitamin D supplementation in 1000 persons over 1 year:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with calcium and vitamin D supplementation
Fracture - Hip (SR: Zhao et al. 2017)(risk per 1000 people over 1 year) follow up: range 4 months to 7 years	17927 (7 RCTs)	⨁⨁⨁⨁ HIGH[a]	**RR 1.09** (0.85 to 1.39)	Study population	
				13 per 1,000	**1 more per 1,000** (2 fewer to 5 more)
				High	
				3 per 1,000	**0 fewer per 1,000** (0 fewer to 1 more)
Fracture - Total (SR: Zhao et al. 2017)(risk per 1000 people over 1 year) follow up: range 4 months to 7 years	10064 (8 RCTs)[b]	⨁⨁⨁⨁ HIGH	**RR 0.90** (0.78 to 1.04)	Study population	
				71 per 1,000	**7 fewer per 1,000** (16 fewer to 3 more)
				High	
				30 per 1,000	**3 fewer per 1,000** (7 fewer to 1 more)
Fracture - Vertebral (Clinical) (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: mean 7 years	36282 (1 RCT)	⨁⨁⨁⨁ HIGH[a,c,d]	**HR 0.90** (0.74 to 1.10)	Study population	
				11 per 1,000	**1 fewer per 1,000** (3 fewer to 1 more)
				High	
				15 per 1,000	**1 fewer per 1,000** (4 fewer to 1 more)
BMD - Multi-site (SR: Tai et	0 (21 RCTs)	⨁⨁◯◯ LOW[e,f]	-	The Systematic Review by Tai et al. (2015) did not directly assess combined Vitamin D + Calcium versus a control or placebo condition,	

This subgroup analysis showed the same findings as the full analysis - suggesting that findings are applicable to a indviduals that may have some differences (dose and frequency of calcium and vitamin d; sex; previous fracture or not; baseline calcium intake; serum vitamin D status). The number of trials for each category is a n of 4 through 8 with a substantial number of events (250 or more events).

It is important to keep in mind that these studies within the SRs have not included individuals receiving pharmacotherapy. Thus, the desirable effects of combined supplementation of calcium and vitamin D may be different in a patient population at high risk of fracture and receiving pharmacotherapy.

al. 2015) assessed with: DXA follow up: range 6 months to 7 years				thus is does not directly answer the research question. Subgroup analysis in this SR compared Calcium supplementation only versus combined Vitamin D + Calcium. Thus, we can only assess the efficacy of Vitamin D supplements in individuals already consuming Calcium. The authors concluded that there were no consistent differences in BMD when comparing Calcium supplementation to combined Vitamin D + Calcium.	
BMD - Muti-site (SR: Reid et al. 2014) assessed with: DXA follow up: range 6 months to 5 years	0 (10 RCTs)[g]	⨁⨁⨁◯ MODERATE[e]	-	The Systematic Review by Reid et al. (2014) did not directly assess combined Vitamin D + Calcium versus a control or placebo condition. Subgroup analysis in this SR compared Vitamin D supplementation only versus combined Vitamin D + Calcium. Thus, we can only assess the efficacy of Calcium supplements in individuals already consuming Vitamin D. The authors concluded that when primary studies reported the additional administration of Calcium to all trial participants there was no observed differences in the BMD outcomes versus Vitamin D supplements only.	
Falls (SR: Bolland et al. 2014b)(risk per 1000 people over 1 year) follow up: range 12 weeks to 3 years	9919 (6 RCTs)	⨁⨁⨁◯ MODERATE[h]	**RR 0.95** (0.89 to 1.03)	Study population	
				353 per 1,000	**18 fewer per 1,000** (39 fewer to 11 more)
				High	
				20 per 1,000	**1 fewer per 1,000** (2 fewer to 1 more)

a. Insufficient number of cases or participants to avoid risk of bias in recommendation of the intervention
b. Similar data reported by Kahwati et al. (2018) for this outcome in males and females (HR: 0.96, CI: 0.91-1.02)
c. Meta-analysis by Kahwati et al. (2018) excluded participants that would be classified as high risk for fracture. "Excluded if participant enrollment was based on known high risk of fracture or falls or if more than 20% of participants had a prior history of Osteoporotic fractures or prevalent fractures at baseline".
d. Studies underpowered for this outcome; not enough evidence to ascertain the influence of dose, route or frequency on incidence

e. Did not directly compare Calcium & Vitamin D to placebo/control
f. Large variation in comparison between Ca and CaD by BMD site (Appendix 2 of Tai et al 2015).
g. This SR did subgroup comparisons with Vit. D alone vs. Vit. D w/ Calcium. The analysis was separated by BMD site and the number of studies included ranged from 2-10.
h. High between-study heterogeneity, authors question validity of subgroup analysis

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

The undesirable effect(s) of combined vitamin D and calcium supplementation were trivial.

This table reports results of the effects of calcium + vitamin D supplementation in 1000 persons over 1 year:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with calcium and vitamin D supplementation
Adverse - Kidney Stones (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: range 4 years to 7 years	39213 (3 RCTs)	⨁⨁⨁⨁ HIGH	**RR 1.18** (1.04 to 1.35)	Study population	
				20 per 1,000	**4 more per 1,000** (1 more to 7 more)
				Low	
				10 per 1,000	**2 more per 1,000** (0 fewer to 4 more)
Adverse - Coronary	0	⨁⨁⨁⨁	**RR 1.01**	Study population	

ADDITIONAL CONSIDERATIONS

Heart Disease (SR: Lewis et al. 2015)(risk per 1000 people over 1 year) follow up: range 1 years to 5.2 years	(4 RCTs)	HIGH	(0.95 to 1.08)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Low	
				60 per 1,000	**1 more per 1,000** (3 fewer to 5 more)
Adverse - Incident Cancer (nonskin)(SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: range 4 years to 7 years	39213 (3 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.73** (0.49 to 1.10)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Low	
				50 per 1,000	**14 fewer per 1,000** (26 fewer to 5 more)
Adverse - Myocardial Infarction (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: mean 7 years	36282 (1 RCT)[a]	⨁⨁⨁⨁ HIGH	**HR 1.03** (0.90 to 1.19)	Study population	
				22 per 1,000	**1 more per 1,000** (2 fewer to 4 more)
				Low	
				25 per 1,000	**1 more per 1,000** (2 fewer to 5 more)
Adverse - Stroke (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year) follow up: mean 7 years	36282 (1 RCT)[a]	⨁⨁⨁⨁ HIGH	**HR 0.95** (0.82 to 1.10)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
				Low	
				30 per 1,000	**1 fewer per 1,000** (5 fewer to 3 more)
Adverse - Venous Thromboembolism (SR: Kahwati et al. 2018)(risk per 1000 people over 1 year)	36282 (1 RCT)[a]	⨁⨁⨁⨁ HIGH	**HR 0.92** (0.79 to 1.07)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
				Low	

follow up: mean 7 years				10 per 1,000	**1 fewer per 1,000** (2 fewer to 1 more)	

a. Data from WHI study (Jackson et al.)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Certainty of fracture data is high and BMD data is moderate. There is moderate certainty in terms of a small desirable effect on fall reduction. For adverse effects, certainty was high for all outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes were decided upon based on results of the Canadian Osteoporosis Patient Network (COPN) survey as well as the perspectives of the diet working group members which included a patient member, a general physician and academic researchers. The main outcomes included the following: -Fracture (and BMD at various skeletal sites was also considered, whether BMD was aligned with/supportive of fracture data) -Falls -Adverse Effects -Quality of Life Because falls are a major cause of fracture and patients identified fracture reduction as an important main outcome there is probably no important uncertainty or variability in how much people value this main outcome.	Results of the Canadian Osteoporosis Patient Network (COPN) survey have been published: Morin et al. Osteoporosis International. 2020;31(5):867-874. Figure 1 from this paper lists outcomes critical to consider in osteoporosis management guideline development. Of note is that this list includes preserving quality of life, preventing fracture and avoiding serious side effects from drugs (reducing falls would be associated with preventing fractures). Each of these was ranked similarly high by respondents. The majority of respondents were patients.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Combined supplementation with calcium and vitamin D does not favour either the intervention or the comparison in terms of fracture, BMD or falls. The fact that individuals had varying levels of baseline vitamin D status and did not experience differences in effect is an important consideration. Canadian data suggests that calcium intakes are not at the recommended level such that supplementation may help some individuals reach appropriate baseline status. There was no data on the effect of combined supplementation with calcium and vitamin D on quality of life.	Intakes of calcium among individuals within studies and between studies can be highly variable and thus above or below the dietary reference intake (DRI) for calcium. Desirable effects of calcium supplementation may be attenuated in individuals with sufficient baseline status (sufficient baseline status is defined as meeting the DRI for calcium). Baseline serum 25OHD (and achieved 25OHD) among individuals within studies and between studies can be highly variable and thus may be below (<50 nmol/L) sufficient status. While it may seem that desirable effects of vitamin D supplementation may be attenuated in individuals with sufficient baseline status (defined as serum 25OHD >50 nmol/L), **subanalysis by baseline serum 25OHD status resulted in a similar result as the full analysis.** (Bolland et al. 2018).

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Calcium and vitamin D supplementation is relatively inexpensive. A calcium supplement (specifically calcium carbonate) containing **500 mg of calcium would cost approximately $0.05 per pill.** A vitamin D supplement containing **1000 IU of vitamin D in the form of 'drops' is $0.10 per drop.** A supplement containing **calcium (500 mg) + vitamin D (200 IU) is $0.05 per pill.** An individual may choose to 'supplement' with calcium or vitamin D using foods. One serving of milk (250 mL) provides approximately **300 mg of dietary calcium and 100 IU vitamin D and costs $0.27 per serving** ($4.39/4 L of skim, 1% or 2% milk). For those who choose not to or cannot consume dairy, several beverages such as orange juice or soy or almond beverages are fortified with calcium and vitamin D. The level of calcium approximates that which is naturally present in cow's milk (300 mg) and the level of vitamin D is lower, at approximately 50 IU per serving in orange juice or 85 IU per serving in soy or almond beverage. Costs are the following: Calcium+vitamin D fortified orange juice: **$0.35 per 250 mL serving** ($2.78/2 L) Calcium+vitamin D fortified soy or almond beverage: **$0.50 per 250 mL serving** ($3.98/2 L). For vitamin D, salmon would represent a food source of vitamin D for Canadians though cost varies as does the vitamin D level. Farmed fish contains much lower levels of vitamin D (approximately 250 IU/serving) compared to approximately 1000 IU per serving for wild salmon. Costs are variable from **$2.60 to $4.40 per 100 g serving for fresh or frozen**. **Canned salmon is less expensive at $2.10 per 100 g serving** and also contains calcium as the bones are softened and can be consumed.	Calcium and vitamin D supplements are less expensive than food sources of calcium and/or vitamin D that contain the largest amounts of these nutrients per serving. These foods include cow's milk as well as foods fortified with calcium+vitamin D such as orange juice or soy or almond beverages. There is no strong evidence that there are differences in bioavailability due to source in terms of benefits to bone health.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	There is high certainty regarding the cost of calcium and vitamin D supplements or obtaining additional calcium and vitamin D through a food source.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost-effectiveness probably does not favour calcium and vitamin D supplementation. Both the cost of calcium and vitamin D supplements and the benefits of supplementation are trivial, but there is additional costs when taking supplements. Food sources may be less desirable for vitamin D due to naturally low levels in many foods. For example, commonly foods containing larger amounts of vitamin D such as salmon (>300 IU/serving) are not widely consumed by Canadians on a regular basis due to a variety of reasons including cost. Milk provides a relatively low level of vitamin D in terms of meeting the RDA but it is among the foods sources that contains high amounts of vitamin D per serving (100 IU/serving).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased	Given the low cost of calcium and vitamin D supplements there would likely be no impact on health equity. If using food sources to increase intake of vitamin D that would be challenging in terms of foods sources and the respective levels per serving and cost is also a consideration. In contrast, food sources of calcium are relatively inexpensive.	

○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, the intervention is acceptable by key stakeholders including patients and health care providers. Supplementation with both calcium and vitamin D supplementation is widely used in Canadian population – there are many commercially-available supplements that contain a combination of these two nutrients because their function in terms of bone health are inter-dependent. Supplementation with both calcium and vitamin D have part of previous recommendations regarding prevention of fracture and also within long term care guidelines for prevention of fracture (Papaioannou et al. Canadian Medical Association Journal. 2015;187(15);1135-1144. Recommendations for preventing fracture in long-term care).	Results of the Canadian Osteoporosis Patient Network (COPN) survey identified interest in understanding how calcium, vitamin D and other nutrients - including vitamin K and protein - can benefit bone health (Morin et al. Osteoporosis International. 2020;31(5):867-874).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Supplements containing both calcium and vitamin D or separately are widely available and relatively inexpensive and have been implemented as part of the prevention and management of fracture guidelines previously.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the**	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
			comparison				
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals meeting calcium recommended dietary allowances with a variety of calcium rich foods, we suggest no supplementation of calcium to prevent fractures.

For individuals who are 50 years and older, we suggest no supplementation of vitamin D beyond Health Canada's recommendation of a 400 IU supplement/day, to prevent fractures.

Justification

Supplementation with combined calcium and vitamin D shows a trivial benefit in terms of reduction of fracture regardless of site (hip, total, vertebral) and this is based on evidence with moderate to high certainty. Undesirable effects were trivial based on moderate to high certain evidence. There were no data about quality of life, another main outcome of interest. Individuals with low baseline intakes of calcium or vitamin D would benefit from supplements to bring them to the RDA that have been established for overall bone health. Adequate intake/status of calcium and vitamin D, together, is important to support bone health. Supplementation with calcium and vitamin D is quite inexpensive. Some individuals may choose to increase calcium and/or vitamin D intake through consumption of calcium rich foods such as milk or beverages that are fortified with calcium and vitamin D.

Subgroup considerations

Implementation considerations

Use of calcium and vitamin D supplements is generally acceptable to Canadians and requires no special implementation considerations. However, for calcium, certain conditions and timing of medication use may necessitate closer consideration.

Monitoring and evaluation

Dietary calcium intake can be estimated. For example, one serving of dairy contains 300 mg of calcium and approximately 300 mg of calcium is consumed by eating a mixed diet as many foods contain small amounts of calcium. There is an upper tolerable level (UL) for calcium of 2000 mg per day for both men and women over age 50 years. Intakes beyond 2000 mg per day have no known benefit to health, including bone health, and can lead to potential adverse effects. For vitamin D, there is an upper tolerable level (UL) of 4000 IU per day for both men and women over age 50 years. Intakes beyond 4000 IU vitamin D per day have no known benefit to health, including bone health, and can lead to potential adverse effects.

Research priorities

QUESTION 4: SHOULD PROTEIN SUPPLEMENTATION VERSUS NO SUPPLEMENTATION BE USED FOR INDIVIDUALS AT INCREASED RISK OF FRACTURE?

Should protein supplementation vs. no supplementation be used for individuals at increased risk of fracture?	
POPULATION:	individuals at increased risk of fracture
INTERVENTION:	protein supplementation
COMPARISON:	no supplementation
MAIN OUTCOMES:	Fracture - Hip; BMD - Multi-site; BMD - Lumbar Spine; Functional - Lean body mass, muscle strength, physical performance; Adverse - Renal Health;
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fractures are associated with significant morbidity and mortality among Canadians. Achieving the recommended dietary allowance (RDA) for protein is important for bone health in healthy populations. Whether intake levels above the RDA through diet or supplementation reduce the prevalence of fracture is of interest to clinicians, patients, and the general population. Moreover, the degree to which protein intake levels are associated with fall risk, quality of life, and adverse outcomes requires more investigation.	The RDA for protein intake is 0.8 mg/kg body weight per day (for both men and women). There is an extensive body of evidence to suggest better musculoskeletal outcomes (particularly for muscle) when higher than recommended levels of protein are consumed in frail individuals. Whether this could apply to individuals at high risk of fracture is important to understand.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	With respect to hip fracture, there is low certainty evidence that protein at or above the current RDA (0.8 g/kg/day) has little to no effect on hip fracture risk. Important to consider that studies are in community dwelling individuals and not individuals who are frail. The desirable effect(s) of protein intake level on BMD are unclear, as comprehensive dose-response data are unavailable and existing studies are heterogenous in study design and treatment.	**Fracture outcome data** includes **hip fracture** and is from the systematic review and meta-analysis from Wallace and Frankenfeld (2017). Data are shown in Figure 2 of the paper: Hip Fracture: RR for Highest versus Lowest Category of Intake. ***A total of 4 different studies were used and all are observational/prospective*. There is no trial data.** A wide range of ages were included.

Age: most studies include individuals >50 y with only one study including men as young as 45 years of age; one SR focuses on older individuals (both men and women, ≥65 years of age) by extracting data for this age group from many of the same cohorts.
Sex: Men are represented in some of the studies.
Follow-up time in observational/cohort studies: The duration of follow-up for most of the studies is quite long. While one study has a follow-up of 1 to 3 years, the other studies include a follow-up period of 6 years, 12 years, 22 years or between 26 (men) and 32 (women) years. These cohorts include the WHI, Nutrses Health Study and Health Professionals Follow-up, Framingham Osteoporosis Study, Iowa Women's Health Study, and National Health and Nutrition Examination Survey (NHANES).
Intakes of protein: Compared highest versus lowest category of protein intake as a percent of energy. Broadly, the following levels of protein intake have been considered within analyses: ≤13%, 13-15% and ≥15% protein by energy (using a 2000 kcal diet this equates to approximately ≤65 g, 65-75 g and ≥ 75 g protein a day. *Of note is that these levels are by no means supplemental levels but rather simply reflect the variation in dietary protein levels as data are from prospective trials. Some of these intakes would be above 0.8 g protein/kg body weight/day.*
Type of protein (animal versus plant): no differences identified but not a lot of data for this comparison.

The following table shows the data from the protein studies:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with protein supplementation
Fracture - Hip (SR: Wallace and Frankenfeld, 2017)(risk per 1000 people over 1 year) follow-up: range 1 years to 32 years	- (6 observational studies)	⨁⨁◯◯ Low	**RR 0.84** (0.73 to 0.95)	High	
				3 per 1,000	**0 fewer per 1,000** (1 fewer to 0 fewer)
Fracture - Hip (SR: Groenendijk et al. 2019)(Older adults, 65-75 years of age)(follow up: range 6 years to 32 years) follow-up: range 6 years to 32 years	- (8 observational studies)	⨁⨁◯◯ Low	**HR 0.89** (0.84 to 0.94)	High	
				3 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
BMD - Multi-site (SR: Koutsofta et	- (5 RCTs)[a]	⨁⨁◯◯	-	This systematic review investigated RCTs that studied the effect of protein	

In older adults (≥65 years of age): A later SR by Groenendijk et al. compared high versus low dietary protein intake and bone health, including fracture. Data are shown in Figure 2 of the paper and show some comparisons of specific older age groups: >65 y, 65-75 y, >75 years and data for men and women. Findings are similar to those of Wallace and Frankenfeld (2017).

	al. 2018)(Protein diets in postmenopausal women with Osteoporosis) follow-up: range 9 weeks to 24 months		Low[b,c]		intake (through diet and/or supplementation) on osteoporosis in postmenopausal women. The between-study heterogeneity in treatments and design did not permit a pooled reporting of outcomes (i.e. meta-analysis). Importantly, there were too few high-quality studies to determine the efficacy of protein intake level in modulating BMD. Importantly, there did not seem to be any evidence that participant protein intake levels were deficient at baseline. In the two largest (and high quality) studies considered, there were site-dependent decreases in BMD observed in the control population, which may confound the results. It is unclear whether the individual studies were sufficiently powered OR of sufficient duration to make reliable conclusions about the effect of protein intake on BMD.	
	BMD - Multi-site (SR: Shams-White et al. 2018)(Animal vs. plant protein and bone health) follow-up: range 6 months to 24 months	- (7 RCTs)[d]	⨁⨁⨁◯ Moderate[e]	-	The review included seven RCTs that compared equal amounts of dietary protein from different sources (i.e. animal vs. plant) and their effect on bone outcomes. All plant sources of protein were from soy, although animal sources were not uniform. Protein doses in the studies ranged from 18-40 g/day, and the amount of supplemental calcium included in the studies varied from 315-1200 mg/day. With respect to mean percentage change in BMD between protein sources, the authors did not observe a significant difference at any of the sites (i.e. Lumbar Spine, Total Hip, Femoral Neck, Total Body), with a C-level ("limited") SOE grading. There was "inadequate" (i.e. D-level) evidence assigned to the effect of protein source on falls and fractures. The authors conclude that there is no support for the concept that soy proteins are more advantageous for bone health outcomes versus animals proteins, or vice versa. Importantly, the review concluded that all studies of	

				protein supplements may have been limited in duration and sample size.	
BMD - Lumbar Spine (SR: Shams-White et al. 2017)(Dietary protein and bone health) follow-up: range 1 years to 2 years	989 (16 RCTs)[f,g,h,i]	⨁⨁⨁◯ Moderate[j,k]	-	The mean BMD - Lumbar Spine (SR: Shams-White et al. 2017)(Dietary protein and bone health) was **0** %	MD **0.52 % higher** (0.06 higher to 0.97 higher)
Functional - Lean body mass, muscle strength, physical performance (SR: Ten Haaf et al. 2018) follow-up: range 6 weeks to 104 weeks	768 (36 RCTs)[l,m]	⨁⨁⨁◯ Moderate[n,o]	-	The mean functional - Lean body mass, muscle strength, physical performance (SR: Ten Haaf et al. 2018) was **0** SD	SMD **0.11 SD higher** (0.06 lower to 0.28 higher)

a. Meta-analysis conducted on 5 RCTs including 677 postmenopausal women aged 50-80 years, and protein intake was either dietary, dietary + supplement (intake range: 51-114 g/day).
b. The number of participants in each study was likely insufficient to achieve statistical power for the analysis (i.e. for three of the studies, no experimental group exceeded n=26). In addition, the protein intake levels among the various studies were not scaled to bodyweight of the participants (i.e. g/kg/day), and were reported in absolute terms (i.e. g/day).
c. Studies included in the analysis were heterogeneous with respect to participants, design, protein administration (i.e. supplement vs diet, or combined), and duration.
d. The review included seven studies that compared equal amounts of dietary protein from different sources (i.e. animal vs. plant). All plant sources of protein were from soy, although animal sources were not uniform and included milk and eggs. Protein doses in the studies ranged from 18-40 g/day, and the amount of supplemental calcium included in the studies varied from 315-1200 mg/day.
e. Sub-analysis of the effect of protein source on BMD at each site was conducted on a limited number of studies (i.e. 2-4) and limited quality of evidence. It is unclear whether the individual studies were sufficiently powered for the comparison of animal vs. plant protein.
f. Studies were heterogeneous in design and target population, including men and women, with and without obesity, and pre/post menopausal. The primary comparison was made between those individuals with higher

	protein intake (i.e. 90 g/day at ~1.4 g/kg/day) versus individuals with lower protein intake (i.e. <80 g/day and ~0.8 g/kg/day). No direct comparisons were made between protein supplementation versus placebo or control. Source (i.e. supplement, diet source, dairy-only) and frequency of protein intake (i.e. 2 vs. 3 servings) were variable. Overall the risk of bias of the included RCTs was medium and low compliance was observed in the participant pools (i.e. <80%), with dropout rate >20%. The authors state that the existing data are too heterogeneous and the evidence is not strong enough to warrant a clinical guideline for increased protein intake. g. The authors also considered seven cohort studies where total protein intake was considered with respect to Lumbar Spine BMD. Six of these studies reported no association between protein intake and LS BMD, and most of the studies did not address whether the reported outcomes were sufficiently powered with respect to sample size. h. In other analysis of pooled Total Hip BMD, meta-analysis of seven RCTs demonstrated a 0.30% change in BMD (CI: -0.02%-0.62%). Additionally, analysis of six RCTs for the effect of protein intake on Femoral Neck BMD resulted in a pooled net-percentage difference of -0.14% (CI: -0.60%-0.32%). i. The authors were unable to find RCTs examining the effect of protein intake on risk of Falls or Fracture (i.e. Spine, Hip, Forearm, Overall) that met the inclusion criteria. j. This meta-analysis did not make a direct assessment of supplemental protein intake versus no supplementation (i.e. diet alone), but rather made pooled comparisons between higher and lower protein intake levels. Moreover, the participants included in the studies were not designated as individuals at higher risk of fracture or with clear protein-insufficiency. k. Risk of bias is elevated due to heterogeneity in the study design and participants included in the studies, as well as the variability in protein source and intake levels studied. In addition, the authors note concern that the duration of the included studies may not have been sufficient for differences to manifest in the outcomes of interest. l. Inclusion characteristics of the study participants were healthy "Older Adults" (i.e. average age ≥50 years) who were nonfrail and community-dwelling (total of 1682 participants). Acceptable protein interventions were those that used oral protein supplementation or a mixture of ≥8 essential amino acid or protein-rich products. m. There was also no observed significant effect of protein supplementation on Muscle Strength (i.e., Handgrip, Leg extension), or Physical Performance (i.e. Gait speed, chair-rise time). n. It is not clear how the current results translate into the reduction of falls and fracture risk. o. There was great heterogeneity in the study design and interventions used in the studies. For example, of the 36 studies used in this analysis, eleven were exclusively male participants, seven were exclusively female, and thirteen included both sexes. Importantly, there were large ranges in habitual protein intake levels among the studies (i.e. ranged from 0.78 to 1.39 g/kg/day), where all but one study demonstrated individuals exceeding the baseline RDA). Protein intervention levels were highly variable as well, and ranged from 3-136 g/day, with varying composition	

and timing of administration.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

With respect to renal health, there was low certainty evidence that protein intakes above the RDA are consistent with normal kidney function. There is limited and inconsistent evidence to determine whether elevated protein intakes and/or protein source are associated with undesirable effects such as kidney stones or renal pathology. Studies that have evaluated this aspect are from relatively short-term intervention studies. However, many Canadians do consume protein above the RDA (0.8 g protein/kg body weight/day) and this does not seem to be associated with compromised renal health.

The following table shows the data from the protein studies:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with protein supplementation
Adverse - Renal Health (SR: Van Elswyk et al. 2018)(Outcomes in individuals with protein intake above the RDA) follow-up: range 4 days to 6 months	0 (18 RCTs)[a]	⨁⨁◯◯ Low[b,c]	-	This study investigated whether protein intake higher than the RDA (i.e. from 20-35% of total energy intake OR ≥10% greater than comparison protein intake) inceased adverse outcomes of kidney function. There was low certainty evidence due to inconsistency for greater risk of kidney stones at higher protein intake levels. Increased protein intake had little to no effect on blood markers of kidney function or blood pressure. There was little data to determine the role that increase protein from a particular source (i.e. plant or animal) influences kidney health. The authors concluded that for the relatively short duration interventions included in the analysis, higher protein intake within the range of recommended intakes for protein are consistent with normal kidney function in healthy individuals.	

ADDITIONAL CONSIDERATIONS

	a. A total of 26 studies were included in the study (18 RCTs and 8 observational studies). b. This review did not directly assess the effect of protein supplementation on renal health, and the participants (>18 years old, healthy) were not at an increased risk of fracture. c. Authors noted that the majority of the clinical trials included in the analysis were of moderate to high risk of bias, and only two of the studies included exceeded 100 subjects.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Certainty of the presented evidence is low to moderate. Of note is that the certainty of evidence for a main outcome, hip fracture, is low and from observational studies. There is moderate evidence for functional measures: muscle strength, physical performance and also lean body mass. There is low certainty evidence for adverse effects on renal health.	Subgroup analysis for source of protein was not possible due to generally low intakes of plant protein. Most protein in studies to date is from animal sources (dairy and non-dairy). The few high quality studies available and high level of heterogeneity in design (i.e. treatment, follow-up) are not sufficient for detailed sub-group analysis or determination of dose-response associations. Habitually higher intakes of protein as identified through observational studies with follow-up for many years (up to 32 years) do not indicate that there is adverse effects of consuming higher dietary levels of protein. Of note is that dietary levels and not supplementary levels are being considered in these propsective studies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes were decided upon based on results of the Canadian Osteoporosis Patient Network (COPN) survey as well as the perspectives of the diet working group members which included a patient member, a general physician and academic researchers. The main outcomes included the following: -Fracture (and BMD at various skeletal sites was also considered, whether BMD was aligned with/supportive of fracture data) -Falls -Adverse Effects -Quality of Life	Results of the Canadian Osteoporosis Patient Network (COPN) survey have been published: Morin et al. Osteoporosis International. 2020;31(5):867-874. Figure 1 from this paper lists outcomes critical to consider in osteoporosis management guideline development. Of note is that this list includes preserving quality of life, preventing fracture and avoiding serious side effects from drugs (reducing

		falls would be associated with preventing fractures). Each of these was ranked similarly high by respondents. The majority of respondents were patients.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The balance of effects does not favour either the intervention or the comparison.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The difference in protein intake from the lowest to highest tertile (this comparison is made in most of the prospective studies) is 12 to 25 g of protein per day depending on baseline intake. Cost can vary widely among sources as detailed below. **Whey Supplement** 1 scoop (approximately 29 g of supplement) contains 17 g of protein. Cost is approximately $1.20 per scoop. **Vegan Supplement** 1 scoop (approximately 27 g of supplement) contains 15 g of protein. Cost is approximately $1.66 per scoop. The source is often 'pea'. **Meal Replacement Drink** Contains approximately 10 -15 g of protein per 237 mL serving depending on whether it is 'regular' or a 'high protein' choice, respectively. Cost is $1.92 or $2.24 per serving. **Food sources** Milk	Important to note that the amounts of protein mentioned in this section (Resources Required) are best estimates that have been calculated. Also, costs associated with various products and sources of protein are also estimates based on current pricing at local grocery chains. The cost for additional protein is variable depending on source. Important to consider that some protein sources may also include additional calcium and vitamin D and thus contribute to bone health.

	9 g protein per serving. Cost is $0.27 per 250 mL serving ($4.39/4 L of skim, 1% or 2% milk). Yogurt 10-12 g protein for greek yogurt per 100 g serving. $1.17 per serving. Chicken 28 g protein per 85 g serving (breast, skinless). $3.07 per serving. Salmon 21-25 g protein per 100 g serving. Cost per 100 g serving ranges from $2.10 to $4.41 depending on source (farmed, wild) and type (fresh, frozen, tinned) Beef 20 g protein per 75 g serving of lean ground beef and the cost is approximately $1.00. 24 g protein per 85 g serving of steak (t-bone) and the cost is approximately $3.60. Beans Variable levels of proteins in beans but can broadly estimate that a 125 gram serving contains 6 to 11 g protein. For mixed beans (kidney beans, chick peas, romano beans, northern white beans in a tin) there is 8 g of protein in a 125 mL serving and the cost is $0.41.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	There is high certainty regarding the cost of protein supplements or obtaining additional protein through a food source. There are many potential sources of protein in the diet so many options available to individuals.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There is a cost to increasing protein intake that should be considered. When deciding on source of protein (food - and within this, type of food or supplements) other bone-supporting nutrients such as calcium and vitamin D can also be considered.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Some sources of protein - either from foods and/or a supplement - may be expensive for some individuals to incorporate on a daily basis. Also, if an individual is not directly making the food purchases it may be more challenging for them to get additional protein through food sources. (see section on Resources Required for more information about costs associated with increasing protein intake)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The use of protein supplements is generally acceptable by key stakeholders, both patients and health care providers. However, consumption of protein foods and supplements must reflect individual dietary patterns and needs and consider overall health including kidney function.	Results of the Canadian Osteoporosis Patient Network (COPN) survey identified interest in understanding how calcium, vitamin D and other nutrients - including vitamin K and protein - can benefit bone health (Morin et al. Osteoporosis International. 2020;31(5):867-874).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Protein supplements are widely available, though factors such as route of ingestion, amino acid profile, quality, and co-consumption with other ingredients add important complexity to decision making, as well as cost. Importantly, for most individuals, it does remain feasible and cost-effective to reach the RDA for protein without supplementation.	

	A serving of milk (250 mL) provides 8 g of protein. Mixed beans provide 8 g of protein per serving. A serving of a commercially available meal replacement provides 10 g protein per serving (237 mL) but high protein option provides 15 g protein per serving. Ground beef and steak provide 20 or 24 g of protein per serving, respectively. Salmon provides 21 to 25 g of protein per serving. Chicken breast provides 28 g of protein per serving. Of note is that some of these sources may also provide substantial levels of calcium and vitamin D to support bone health: milk, yogurt, meal replacements, whey supplement. The ongoing debate and investigation of the health implications of protein source (i.e. protein from animal, plant, or dairy) is of prime importance, and may contribute to the assessment of acceptibility and feasibility of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals who follow Canada's Food Guide, we suggest no supplementation of protein, vitamin K or magnesium to prevent fractures.

Justification

There is low certainty for trivial benefits or harms with higher protein intakes. Studies have been performed in people who are likely well nourished. There is no evidence of harm to bone health when higher levels of protein are habitually consumed through dietary sources and there is uncertainty about kidney health. Most individuals should be able to achieve protein intakes above the RDA without supplementation.

Subgroup considerations

Insufficient data to conclude that protein source matters (dairy, other animal, plant)

Implementation considerations

Monitoring and evaluation

Approaches for estimating and/or measuring protein intake, as well as assessment of baseline status, are critical tools for future work in this field.

Research priorities

Protein supplementation should be studied in RCTs with fracture as an outcome.

Given the emphasis of plant based proteins in the new Canada food guide, understanding if protein source has different effects on on bone health (i.e. animal versus plant versus dairy), controlling for the effects of non-protein modulation of bone via other bioactives

QUESTION 5: SHOULD MAGENESIUM SUPPLEMENTATION VERSUS NO SUPPLEMENTATION BE USED FOR INDIVIDUALS AT INCREASED RISK OF FRACTURE?

Should magnesium supplementation vs. no supplementation be used for individuals at increased risk of fracture?	
POPULATION:	individuals at increased risk of fracture
INTERVENTION:	magnesium supplementation
COMPARISON:	no supplementation
MAIN OUTCOMES:	Fracture - Hip; Fracture - Total; Fracture - Lower Arm & Wrist; BMD - Multisite; Serum Magnesium;
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fractures are associated with significant morbidity and mortality among Canadians. Achieving the recommended dietary allowance (RDA) for magnesium is important for bone health in healthy populations. Whether intake levels above the RDA through supplementation reduce the prevalence of fracture is of interest to clinicians, patients, and the general population. Moreover, the degree to which magnesium intake levels are associated with fall risk, quality of life, and adverse outcomes requires more investigation.	The RDA for magnesium for adults over age 50 years is 320 mg (females) or 420 mg (males). Main dietary sources are the following: green leafy vegetables, legumes, nutrs, seeds, whole grains. The upper tolerable limit (UL) for magnesium is 350 mg though this value is actually lower than the recommended level for males over age 50 years - this is because the UL tolerable upper limit has been set at the level where any individual experiences even mild stomach or intestinal distress.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate	We found no studies comparing magnesium supplementation to no supplementation. We found a large observational study (Women's Health Initiative - Orchard et al. American Journal of Clinical Nutrition. 2014;99(4):926-933) where total magnesium intake was estimated from food records and supplements	The evidence is low certainty for trivial to no differences in hip fractures, total fractures and lower arm and wrist fractures, and falls. There may also be little to no correlation between BMD and

○ Large ○ Varies ○ Don't know	and the highest quintile of the cohort (≥422.5 mg/day) was compared to the lowest (<206.5 mg/day).	magnesium intake levels based on very low certainty evidence. Another study in postmenopausal women assessed the association of serum magnesium levels with osteoporosis but was used as indirect evidence. Low certainty evidence shows that lower serum magnesium may be associated with osteoporosis.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with magnesium supplementation
Fracture - Hip (SR: Farsinejad et al. 2016)(Data Source: Orchard et al. 2014)(risk per 1000 people over 1 year) follow-up: mean 7.6 years	29413 (1 observational study)[a,b]	⨁◯◯◯ Very low[c]	**HR 1.04** (0.81 to 1.34)	High	
				3 per 1,000	**0 fewer per 1,000** (1 fewer to 1 more)
Fracture - Total (SR: Farsinejad et al. 2016)(Data Source: Orchard et al. 2014)(risk per 1000 people over 1 year) follow-up: mean 7.6 years	29413 (1 observational study)[a,b]	⨁◯◯◯ Very low[c]	**HR 1.01** (0.95 to 1.08)	High	
				30 per 1,000	**0 fewer per 1,000** (1 fewer to 2 more)
Fracture - Lower Arm & Wrist (SR: Farsinejad et al. 2016)(Data Source: Orchard et al. 2014)(risk per 1000 people over 1 year) (note: number of fractures are	29413 (1 observational study)[a,b]	⨁◯◯◯ Very low[c,d]	**HR 1.23** (1.07 to 1.42)	High	
				20 per 1,000	**5 more per 1,000** (1 more to 8 more)

trivial) assessed with: Self-reported follow-up: mean 7.6 years					
BMD - Multisite (SR: Farsinejad et al. 2016)	- (9 observational studies)	⨁◯◯◯ Very low[e,f]	-	Farsinejad et al. (2016) conducted a meta-analysis from primary data sources with mixed study design that correlated magnesium intake (diet and supplemental) with BMD. For Total Hip BMD in 1430 participants (3 studies) there was a marginally significant correlation with magnesium intake (r : 0.16, CI : 0.00-0.32). For Femoral Neck BMD in 2837 participants (8 studies) there was a marginally significant correlation with magnesium intake (r : 0.14, CI : 0.00-0.28). For Lumbar Spine BMD in 1950 participants (6 studies) there was no significant correlation with magnesium intake observed (r : 0.09 CI : -0.01-0.19). Followup measures in the individual studies ranged from 1 to 7.6 years, and significant between-study heterogeneity was calculated for all BMD site-specific analyses.	
Falls (≥2 falls in past year)(Data Source: Orchard et al. 2014)(risk per 1000 people over 1 year) (note: number of falls are trivial) follow-up: mean 7.6 years	29413 (1 observational study)[a,b]	⨁◯◯◯ Very low[c,d]	**HR 1.15** (1.10 to 1.20)	High	
				20 per 1,000	**3 more per 1,000** (2 more to 4 more)
Serum Magnesium (SR: Zheng et al. 2014)	- (12 observational studies)	⨁◯◯◯ Very low[g,h,i]	-	In a pooled meta-analysis of 12 case-control study arms involving 1349 postmenopausal women, significantly lower serum magnesium levels were measured in those with osteoporosis (vs.	

				healthy Control). The standardized mean difference was -0.55 mg/dl (CI: -0.83 to -0.26). Sub-analysis of the data revealed no differences in the observed effect for participants aged <60 or >60. The authors concluded that low serum levels of magnesium may be a risk factor for osteoporosis in postmenopausal women, although it is unclear how geographical differences may have contributed to the significant between-study heterogeneity. The authors suggest that controlled trials are necessary to elucidate the potential causal relationship between serum magnesium levels and postmenopausal osteoporosis.

a. Orchard et al. (2014) did not have a control/placebo vs. supplement intervention. Rather, they used intake records to form quintiles by total magnesium intake (diet + supplemental). Data included in this table compare the lowest quintile (<206.5mg/day) to the highest quintile (≥422.5mg/day). Average intake in the cohort was 335 mg/day (RDA: 310-320 mg/day) and 85% of the intake was obtained from diet (remainder from supplements).
b. Data from the WHI Observational Study (73,684 postmenopausal women aged 50-79 between 1994-1998).
c. There was no control/placebo group to assess the potential effect of magnesium intake. Total magnesium intake used instead of magnesium supplements.
d. The authors suggested that the increase in falls with higher levels of magnesium intake might be the result of differences in activity levels within the quintiles of analysis. This observation could represent an important causal link to the observed increase in Lower-arm & Wrist Fractures.
e. Significant between-study heterogeneity was calculated for each BMD site analysis. Magnesium intake was diet + supplemental with a wide range of intervention designs and follow-up. Significant correlations between magnesium intake and BMD do not provide clinical estimates of the absolute effect on density measurements within each participant. Correlation estimates do not provide improve our causative relationship of dietary magnesium levels and BMD.
f. Mean age of the participants in the individual studies ranged from 20-74 years, and there was no reported baseline BMD values to assess fracture risk amongst participants.
g. Caution should be exercised when interpreting the reported relationship between postmenopausal osteoporosis and serum magnesium, as it does not provide causal evidence of an effect to any of the primary outcomes of interest in this analysis (i.e. fracture, BMD, falls). Moreover, there are additional methodological and geographical concerns that contribute to the increased risk of bias evaluation (see points h, i, and j).

	h. The authors observed significant heterogeneity in the studies and specifically noted geographical differences in subgroup analysis (studies were from Belgium, Turkey, and China). i. The potential causal relationship between serum magnesium levels and postmenopausal osteoporosis remains unclear.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	There was no evidence from studies measuring adverse effects of magnesium.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Certainty of evidence for these outcomes is universally very low and does not represent controlled studies where magnesium supplementation interventions are directly compared to matched control/placebo cohorts	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability	The main outcomes were decided upon based on results of the Canadian Osteoporosis Patient Network	Results of the Canadian Osteoporosis Patient Network (COPN)

○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	(COPN) survey as well as the perspectives of the diet working group members which included a patient member, a general physician and academic researchers. The main outcomes included the following: -Fracture (and BMD at various skeletal sites was also considered, particularly whether BMD aligned with or was supportive of fracture data) -Falls -Adverse Effects -Quality of Life There was no important uncertainty about or variability in how much people value the main outcomes. Patients identified fracture reduction as an important main outcome.	survey have been published: Morin et al. Osteoporosis International. 2020;31(5):867-874. Figure 1 from this paper lists outcomes critical to consider in osteoporosis management guideline development. Of note is that this list includes preserving quality of life, preventing fracture and avoiding serious side effects from drugs (reducing falls would be associated with preventing fractures). Each of these was ranked similarly high by respondents. The majority of respondents were patients.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is very low certainty that there is little to no difference in benefits or harms with supplementation of magnesium.	In the primary study used in the analysis, mean magnesium intake level of the whole cohort was 335 mg/day, which is slightly above the DRI (320 mg/day for women; 420 mg/day for men), with ≥85% of the estimated total intake from dietary sources.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Magnesium supplementation is relatively inexpensive. A magnesium supplement containing **250 mg of magnesium would cost approximately $0.60 per pill.** Magnesium is present in many foods with highest levels in nuts, seeds and green leafy vegetables.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ● High ○ No included studies	There is high certainty regarding the cost of magnesium supplements or obtaining additional magnesium through a food source.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost-effectiveness does not favor either the intervention or the comparison. Although the cost of magnesium supplementation is negligible it is still a cost, and therefore cost effectivess probably favours not providing supplementation.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Given the low cost of magnesium supplements and that magnesium can be obtained through food sources relatively inexpensively, there would likely be no impact on health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The use of magnesium supplements is likely acceptable by key stakeholders, both patients and health care providers.	Results of the Canadian Osteoporosis Patient Network (COPN) survey identified interest in understanding how calcium, vitamin D and other nutrients - including vitamin K and protein - can benefit bone health (Morin et al. Osteoporosis International. 2020;31(5):867-874).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Magnesium supplements are widely available and relatively inexpensive, thus are feasible to implement. Moreover, it is feasible to reach the recommended RDA through dietary intake with targeted food choices and planning.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the	Probably favors the intervention	Favors the intervention	Varies	No included studies

	JUDGEMENT						
			comparison				
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals who follow Canada's Food Guide, we suggest no supplementation of protein, vitamin K or magnesium to prevent fractures.

Justification

There is very low certainty of evidence for trivial to no differences in benefits or harms of magnesium supplementation. However, there may be an association of low serum levels with osteoporosis. Although the cost of supplements is negligible, it would be an unnecessary cost and burden given that there may be no benefits.

Subgroup considerations

Implementation considerations

Use of supplements is generally acceptable to Canadians and requires no special implementation considerations.

Monitoring and evaluation

Research priorities

- Controlled studies of supplementation with dietary intake controls
- Baseline status analysis and causative link of serum levels to bone health

QUESTION 6: SHOULD VITAMIN K SUPPLEMENTATION VERSUS NO SUPPLEMENTATION BE USED IN INDIVIDUALS AT INCREASED RISK OF FRACTURE?

Should vitamin K (noting isoforms) supplementation vs. no supplementation be used for individuals at increased risk of fracture?	
POPULATION:	individuals at increased risk of fracture
INTERVENTION:	vitamin K (noting isoforms) supplementation
COMPARISON:	no supplementation
MAIN OUTCOMES:	Fracture - Hip; Fracture - Total; Fracture - Total; BMD - Lumbar Spine; BMD - Femoral Neck; BMD - Lumbar Spine; Serious Adverse Outcomes;
SETTING:	Community
PERSPECTIVE:	Population
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fractures are associated with significant morbidity and mortality among Canadians. Achieving the recommended intake (adequate intake, AI) for vitamin K is important for bone health in healthy populations. Whether intake levels above the RDA through diet or supplementation reduce the prevalence of fracture is of interest to clinicians, patients, and the general population. Moreover, the degree to which vitamin K intake levels are associated with fall risk, quality of life, and adverse outcomes requires more investigation.	Vitamin K refers to a group of vitamins that share a similar chemical structure. The two main forms in the diet are vitamin K1 and vitamin K2. The AI for Vitamin K for adults over age 19 years is 90 ug (females) or 120 ug (males). Vitamin K1 is plentiful in the diet if regularly consuming leafy greens (examples include kale, brocolli, spinach) Vitamin K2 is present in fermented foods and animal food sources and there are synthetic forms of vitamin K2 (menatetrenone). K2 is also produced by bacteria. Natto (fermented soybean) contains a significant level of vitamin K2 (1062 ug per 100 g). Other sources with much lower quantities include egg yolk, cheeses, pork and chicken.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Vitamin K intake, whether through supplemental menatetrenone or total estimated dietary intake, may result in a small decrease in fracture risk. Controlled trials with menatetrenone (K2) provide very low or low certainty evidence that, when compared to control/placebo, supplementation may result in an important decrease hip or total fractures, respectively. These findings were consistent with moderate to high certainty evidence that a variety of different vitamin K interventions likely results in trivial to small increases in BMD at the lumbar spine and femoral neck. There is no data for vertebral fractures, falls, and quality of life. The following table shows the data from the vitamin K1 and K2 studies:	Direct comparison of the differences in the effects between the various vitamin K isoforms is problematic due to the underlying differences between supplements provided in controlled trials versus dietary intake analysis. Also, the populations studied for vitamin K2 are at high risk of fracture. Also of note are the differences in baseline diet in the Asian diet versus Canadian diet - more fermented foods and thus vitamin K2 in baseline diet. **Vitamin K2 & fracture (fractures per 1000 persons over 1 year): 2 fewer hip fractures per 1000 persons over 1 year** and this is a greater reduction than the threshold of 1 less hip fracture that has been set as desirable by the Steering Committee and Working Groups. Also, 7 fewer total fractures is reported and this is the same as the threshold of 7 fewer total fractures that has been set as desirable by the Steering Committee and Working Groups. These findings are in women and mostly post-menopausal women (age 53-75 years). **Vitamin K1:** No data on hip fracture. These findings are in men and women, age 30 years and older. Intake determined from food records. Comparison made between lowest and highest quartiles for dietary intakes.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with vitamin K (noting isoforms) supplementation
Fracture - Hip (SR: Su et al. 2019)(Supplemental menatetrenone, Vitamin K2)(risk per 1000 people over 1 year)(All have diagnosed OP; in 1 trial unclear what previous OP treatment received previously) follow-up: range 6 months to 4 years	322 (2 RCTs)[a]	⨁◯◯◯ Very low[b,c]	**RR 0.26** (0.03 to 2.33)	Study population	
				18 per 1,000	**13 fewer per 1,000** (18 fewer to 24 more)
				High	
				3 per 1,000	**2 fewer per 1,000** (3 fewer to 4 more)
Fracture - Total (SR: Hao et al. 2017)(Dietary Intake, Vitamin K1)(risk per 1000 people over 1 year) follow-up: range 6.9 years to 10 years	80982 (5 observational studies)[d,e]	⨁⨁◯◯ Low[f]	**RR 0.78** (0.56 to 0.99)	High	
				30 per 1,000	**7 fewer per 1,000** (13 fewer to 0 fewer)
Fracture - Total (SR: Su et al. 2019)(Supplemental menatetrenone, Vitamin K2)(risk per 1000 people over 1 year)	6079 (3 RCTs)[a]	⨁⨁◯◯ Low[g]	**RR 0.78** (0.48 to 1.25)	Study population	
				62 per 1,000	**14 fewer per 1,000** (32 fewer to 15 more)
				High	

follow-up: range 6 months to 4 years				30 per 1,000	**7 fewer per 1,000** (16 fewer to 8 more)
BMD - Lumbar Spine (SR: Fang et al. 2012)(Supplemental Vitamin K, all isoforms) assessed with: DXA follow-up: range 6 months to 36 months	2036 (13 RCTs)[h]	⨁◯◯◯ Very low[i,j,k]	-	The mean BMD - Lumbar Spine (SR: Fang et al. 2012)(Supplemental Vitamin K, all isoforms) was **0** %	MD **1.27 % higher** (0.47 higher to 2.06 higher)
BMD - Femoral Neck (SR: Fang et al. 2012). (Supplemental Vitamin K, all isoforms) assessed with: DXA follow-up: range 6 months to 36 months	1271 (6 RCTs)[h]	⨁◯◯◯ Very low[i,k]	-	The mean BMD - Femoral Neck (SR: Fang et al. 2012). (Supplemental Vitamin K, all isoforms) was **0** %	MD **0.17 % higher** (0.21 lower to 0.54 higher)
BMD - Lumbar Spine (SR: Su et al. 2019)(Supplemental menatetrenone, Vitamin K2) follow-up: range 6 months to 4 years	512 (5 RCTs)[a]	⨁⨁◯◯ Low[i]	-	The mean BMD - Lumbar Spine (SR: Su et al. 2019)(Supplemental menatetrenone, Vitamin K2) was **0** %	MD **2.11 % higher** (0.91 higher to 3.32 higher)

a. Participants were adults aged ~45-75, menatetrenone treatment (45 mg/day) with and without other treatments.
b. Women had been previously diagnosed with osteoporosis. Some may have received prior treatment though that information is not provided. This is population at high/very high risk of fracture.
c. In the absence of any hip fracture events in the intervention group, the calculation of a relative effect related to the intervention is potentially misleading.
d. Meta-analysis included four cohort studies and one nested case-control study (men and women, age range 30-94), total of 1114 recorded fractures in 80,982 participants. Dietary Vitamin K intake was estimated from FFQ and food records; therefore, intake level refers almost exclusively to phylloquinone (Vitamin K1). In each study, RR values represent the highest level of dietary Vitamin K intake (quartile/quintile) compared against the lowest intake level.
e. The authors also conducted a Dose-Response meta-analysis to produce a

	pooled RR of fracture for an increase in 50ug dietary Vitamin K intake per day (RR: 0.97, CI: 0.95-0.99). f. There was no Vitamin K supplementation intervention in the included studies, with all Vitamin K intake values estimated from dietary intake. g. Women have previously been diagnosed with osteoporosis and thus are at very high/high risk of fracture. h. Inclusion criteria: participant age ≥18 yrs, BMD by DXA, baseline and endpoint measurements, clearly described Vitamin K dose (all isoforms), and duration of study >6 months. i. Women had been previously diagnosed with osteoporosis. Some may have received prior treatment though that information is not provided. This is population at high/very high risk of fracture. j. Sub-analysis for effect of Vitamin K on BMD at Lumbar Spine noteworthy. For example, Participant Region was a factor, as studies conducted in the west (7 studies, Mean: -0.21, CI: -0.53-0.11) were different from those conducted in Asia (6 studies, Mean: 2.90, CI: 1.77-4.03). Effect was also different when Vitamin K isoforms analyzed, with Vitamin K2 (10 studies, Mean: 1.80, CI: 0.87-2.75) greater than Vitamin K1 (4 studies, Mean: -0.36, CI: -0.77-0.05). Finally, when studies were limited to those including Postmenopausal Women, the significant effect of the intervention on relative BMD was reduced (8 studies, Mean: 0.47, CI: -0.39-1.32). k. Risk of bias was assessed and study quality was considered. However, there was heterogeneity in the meta-analysis and suspected publication bias. For Lumbar Spine analysis, when only the high quality studies were included, these concerns disappeared. Additionally, four of the studies included in the meta-analysis were aimed at participants with diseases or those taking drugs which may effect BMD.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	With respect to undesirable effects, there was high certainty evidence that supplemental menatetrenone (45 mg/day) in adults aged ~45-75, and may result in a trivial reduction in serious adverse events when compared to no supplementation. The following table shows the data from studies providing vitamin K2 supplements:	

Outcomes	№ of	Certainty of	Relative	Anticipated absolute effects* (95% CI)

	participants (studies) Follow up	the evidence (GRADE)	effect (95% CI)	Risk with no supplementation	Risk difference with vitamin K (noting isoforms) supplementation
Serious Adverse Outcomes (SR: Su et al. 2019)(Supplemental menatetrenone, Vitamin K2) follow up: range 6 months to 4 years	5905 (2 RCTs)[a]	⨁⨁◯◯ LOW[b]	**RR 0.96** (0.77 to 1.20)	Study population	
				52 per 1,000	**2 fewer per 1,000** (12 fewer to 10 more)

a. Participants were adults aged ~45-75, menatetrenone treatment (45 mg/day) with and without other treatments.
b. No clear discussion of what these outcomes included.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Certainty of the evidence was generally low. For studies investigating vitamin K2 on fracture there were sometimes very few events resulting in imprecise results. For studies investigating vitamin K1 on fracture there were prospective studies that measured dietary levels of vitamin K1 and there were no clinical trials in which subjects were randomized to vitamin K1 supplementation.	Studies with vitamin K2 (menatetrenone, a synthetic form of vitamin K2) were studied with and without other interventions, such as calcium, vitamin D, alfacalcidol, and sodium etindronate. **Major concerns limiting applicability of findings:** i. Studies have included a very select population in which women have OP indicating they are likely at higher risk for fracture than the average age-matched population. Women may have already been treated for OP prior to enrollment in trials. Past use of osteoporosis medications was sometimes uncertain within studies. ii. There is a very small number of fractures that skews conclusion.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The main outcomes were decided upon based on results of the Canadian Osteoporosis Patient Network (COPN) survey as well as the perspectives of the diet working group members which included a patient member, a general physician and academic researchers. The main outcomes included the following: -Fracture (and BMD at various skeletal sites was also considered, particularly whether BMD aligned with or was supportive of fracture data) -Falls -Adverse Effects -Quality of Life There was no important uncertainty about or variability in how much people value the main outcomes. Patients identified fracture reduction as an important main outcome.	Results of the Canadian Osteoporosis Patient Network (COPN) survey have been published: Morin et al. Osteoporosis International. 2020;31(5):867-874. Figure 1 from this paper lists outcomes critical to consider in osteoporosis management guideline development. Of note is that this list includes preserving quality of life, preventing fracture and avoiding serious side effects from drugs (reducing falls would be associated with preventing fractures). Each of these was ranked similarly high by respondents. The majority of respondents were patients.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Based on low certainty evidence Vitamin K2 supplementation does not favor either the intervention or the comparison. The certainty of the evidence is based primarily on the indirectness of the evidence. For example: geographical location, population studied is at high risk of fracture, and the use of dietary and supplements in studies for vitamin K2 or K1. The undesirable effects of vitamin K2 supplementation are trivial. Studies of vitamin K1 and fracture are limited to prospective studies in which dietary and not supplemental levels of vitamin K1 are studied. There was no data on the effect of vitamins K1 or vitamin K2 on vertebral fractures, falls or quality of life.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Vitamin K2 supplementation is relatively inexpensive. A vitamin K2 supplement containing **120 ug vitamin K2 costs approximately $0.50 per pill.** An individual may choose to 'supplement' with vitamin K using foods though to reach the level of vitamin K2 studied in the RCTs would not be possible - a dose of 45 mg vitamin K2/day has been studied. The AI for Vitamin K for adults over age 19 years is 90 ug (females) or 120 ug (males). There isn't overt evidence that Canadians are not meeting the recommended intake. Vitamin K1 is present in the following foods, expressed as amounts per 1 cup of cooked greens (of note is that each serving of the foods below provides in excess of the AI for vitamin K): Kale: 1062 ug. Spinach: 889 ug. Collard green: 1059 ug.	

	Broccoli: 220 ug Brussels sprouts: 218 ug Vitamin K2 is present in the following foods, expressed as amounts per 100 g: Natto: 1062 ug Cheeses: 57-76 ug Chicken: 60 ug Pork chop: 75 ug Pork sausage: 383 ug	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	There is high certainty regarding the cost of vitamin K2 supplements or obtaining additional vitamin K (either K1 or K2) through a food source.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Although the cost of increasing the intake of vitamin K through supplementation (K2) or diet (K1) is inexpensive, it is an additional cost compared to the uncertain small benefits on some fractures.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Given the fairly low cost of vitamin K2 supplements and that vitamin K1 can be obtained through food sources relatively inexpensively, there would likely be no impact on health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The use of vitamin K supplements is generally acceptable by key stakeholders, both patients and health care providers.	Results of the Canadian Osteoporosis Patient Network (COPN) survey identified interest in understanding how calcium, vitamin D and other nutrients - including vitamin K and protein - can benefit bone health (Morin et al. Osteoporosis International. 2020;31(5):867-874).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	VItamin K supplements are widely available and relatively inexpensive, thus are feasible to implement and are currently part of the clinical management of osteoporosis in certain regions around the world (since 1995 in Japan).	'Dosing' of dietary intake for individuals is potentially challenging. There may be important regional differences in these interventions (many studies in Asia rather than Europe or North America).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals who follow Canada's Food Guide, we suggest no supplementation of protein, vitamin K or magnesium to prevent fractures.

Justification

There is very low to low certainty evidence for small benefits of dietary or vitamin K supplementation for hip or total factures. There is no evidence for vertebral fractures, falls or quality of life. While there may be no serious adverse events and low costs, there are additional costs, and therefore it is suggested to not take vitamin K supplements. Vitamin K2 has been studied as a supplement in a few trials investigating fracture though these studies are in women with a previous diagnosis of osteoporosis and prior treatments for osteoporosis are not considered within these studies and may confound outcomes. With respect to vitamin K1, studies are limited to prospective studies that have assessed diet levels (rather than supplemental levels of vitamin K1) and the association with fracture by comparison of individuals in the lowest and highest quartile of vitamin K1 intake. Vitamin K1 intake has been estimated using dietary questionnaires though there can be challenges with accuracy of intake for this nutrient using such questionnaires. There is currently no evidence directly comparing the efficts of vitamin K consumed through diet (primarily K1) versus supplemental K2 for management of fracture risk and bone health.

Subgroup considerations

Meeting vitamin K requirements (and particularly vitamin K2) may be easier in some cultures in which there is a high consumption of fermented foods.

Implementation considerations

Use of supplements is generally acceptable to Canadians and requires no special implementation considerations.

Monitoring and evaluation

Accurate assessment of dietary vitamin K intakes, particularly in terms of isoform (K1, K2) is challenging but can be estimated from a diet recall.

Research priorities

- How to determine baseline status of vitamin K and classifying deficiency
- Differentiating outcomes by vitamin K isoform and producing high quality evidence of diet versus supplement
- Regional patterns of freq. and design of Vit. K trials (Asia vs. North america vs. Europe).
- Study design heterogeneity is a major challenge when summarizing expected outcomes.

QUESTION 1A: SHOULD A POPULATION-BASED SCREENING STRATEGY USING FRACTURE RISK VS. TARGETED CASE-FINDING BE USED FOR REDUCING THE RISK OF OSTEOPOROTIC FRACTURE?

Should a population-based screening strategy using fracture risk vs. targeted case-finding be used for reducing the risk of osteoporotic fractures?	
POPULATION:	reducing the risk of osteoporotic fractures
INTERVENTION:	a population-based screening strategy using fracture risk
COMPARISON:	targeted case-finding
MAIN OUTCOMES:	Hip fractures, offer to screen in selected populations and acceptors of screening, women over age 65; Major osteoporotic fractures, women over age 65, offer to screen; All osteoporotic fractures, offer to screen in selected populations and acceptors of screening, women over age 65; All cause mortality, offer to screen, women over age 65;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The decision to recommend or not recommend population screening for the purpose of identifying women and men older than 50 y at high risk of osteoporotic fracture has potential to shape government policy and large segments of health care resources in each province. Clinicians and the patients value screening with the goal to prevent negative health outcomes; even if there are associated costs. There is not a lot of guidance in men	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate	The evidence largely arises from 3 large prospective RCTs done in postmenopausal women. In each of the RCTs, there is substantial therapeutic "drop-in" i.e. use of anti-fracture medications in the control arms which may have significantly impaired the study's ability to see a beneficial effect. We have identified a systematic review and meta-analysis	

○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with targeted case-finding	Risk difference with a population-based screening strategy
Hip fractures, offer to screen in selected populations and acceptors of screening, women over age 65	42009 (3 RCTs)	⨁⨁⨁⨁ High[a]	**HR 0.80** (0.71 to 0.91)	Study population	
				27 per 1,000	**5 fewer per 1,000** (8 fewer to 2 fewer)
Major osteoporotic fractures, women over age 65, offer to screen	29526 (3 RCTs)	⨁⨁⨁⨁ High[a]	**HR 0.91** (0.84 to 0.98)	Study population	
				84 per 1,000	**7 fewer per 1,000** (13 fewer to 2 fewer)
Clinical fragility fractures, offer to screen in selected populations and acceptors of screening, women over age 65	42009 (3 RCTs)	⨁⨁⨁⨁ High[a]	**HR 0.95** (0.89 to 1.00)	Study population	
				117 per 1,000	**6 fewer per 1,000** (12 fewer to 0 fewer)
All cause mortality, offer to screen, women over age 65	23404 (3 RCTs)	⨁⨁⨁⨁ High[a]	**HR 1.04** (0.95 to 1.14)	Study population	
				86 per 1,000	**3 more per 1,000** (4 fewer to 11 more)

a. The participation rates to the screening programs in the three studies ranged from 34 to 61% and an additional 8 to 25% of the participants dropped out before examination. During follow-up, the difference in received treatment between the screening groups and the usual care groups was reduced by non-adherence and an increase of usual care prescriptions in the control group. This treatment contrast declined to 3.5–8% after 3.7 to 5 years.

(Merlijn et al., 2020)

We also conducted additional analyses using a large Canadian population –based registry of in males and females 50 y and older.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with targeted case-finding	Risk difference with a population-based screening strategy
Hip fractures, offer to screen in selected populations and acceptors of screening, women over age 65	42009 (3 RCTs)	⨁⨁⨁⨁ High[a]	**HR 0.80** (0.71 to 0.91)	Study population	
				27 per 1,000	**5 fewer per 1,000** (8 fewer to 2 fewer)
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Clinical fragility fractures, offer to screen in selected populations and acceptors of screening, women over age 65	42009 (3 RCTs)	⨁⨁⨁⨁ High[a]	**HR 0.95** (0.89 to 1.00)	Study population	
				117 per 1,000	**6 fewer per 1,000** (12 fewer to 0 fewer)
All cause mortality, offer to screen, women over age 65	23404 (3 RCTs)	⨁⨁⨁⨁ High[a]	**HR 1.04** (0.95 to 1.14)	Study population	
				86 per 1,000	**3 more per 1,000** (4 fewer to 11 more)

a. The participation rates to the screening programs in the three studies ranged from 34 to 61% and an additional 8 to 25% of the participants dropped out before examination. During follow-up, the difference in received treatment between the screening groups and the usual care groups was reduced by non-adherence and an increase of usual care prescriptions in the control group. This treatment contrast declined to 3.5–8% after 3.7 to 5 years.

(Merlijn et al., 2020)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	The evidence if of moderate certainty in females 65 and older that screening reduces hip fractures SALT trial (2019) - 20.7% of screened were treated vs 5.3% of controls SCOOP trial (2018) - 23.8% of screened were treated vs 15.7% of controls ROSE trial (2018) - 23% of screened were treated vs 18% of controls

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Morin SM, Djekic-Ivankovic M, Funnell L, Chepesiuk R, Giangregorio L, Braganca Rodrigues I, Ridout R, FeldmanS, Kim S, McDonald-Blumer H, Kline GA, Ward WE, Santesso N, Leslie WD. Patient Engagement in Clinical Guidelines Development: Input from > 1000 Members of the Canadian Osteoporosis Patient Network (Osteoporosis Int 2019) -- identifies fracture prevention as a most important outcome among people at risk with osteoporosis. In this survey, over 60% of respondents felt that Initial screening with BMD of critical to consider. In on-going WG discussion, both males and females patient partners felt this to be of critical importance for both males and females	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	See table above; actual risks of screening have not been seen and/or reported but no impact on patient quality of life. However, strategies incorporating DXA-BMD have costs and in the absence of meaningful fracture benefit from screening, the balance of effects likely favours no screening if DXA-BMD is involved.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Turner DA et al. The Cost-effectiveness of screening in the community to reduce osteoporotic fractures in older women in the UK: Economic evaluation of the SCOOP Study JBMR 2018;33:845-851. Based on the SCOOP study which showed a small reduction in hip fractures among a high risk subgroup of women undergoing a 2 step screening program. QALY and cost-effectiveness analysis was based on a UK NHS payer model where the anti-fracture drug intervention was assumed to be alendronate; the cost of alendronate was essentially less than 10 GBP for the course of the study. The total cost of the screening program was estimated at 104 GBP per person. The estimate of incremental QALY was 0.0237 per person but the confidence interval overlapped with 0. The incremental cost-effectiveness ratio was 22,067 GBP per hip fracture prevented. Costs set by UK data not necessarily applicable to Canada and assumes intervention was with almost zero-cost oral bisphosphonate

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	No Canadian data on cost-effectiveness of an osteoporosis screening program based on RCT evidence	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	See comments on SCOOP study above; for all fractures, the authors claim that there would be an 83% chance that screening/intervention would be cost-effective (UK setting) at a threshold of 20,000 GBP/QALY. As above; economic analysis of SCOOP uses UK data and assumes almost no cost to anti-fracture drug intervention. The magnitude of actual benefit is very small but would see large numbers of patients undergoing screening.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	A two-step screening program using DXA-BMD was employed in each of the 3 large prospective RCTs. Replication in clinical practice would require a major primary care KT initiative and support (as provided in the ROSE trial) in osteoporosis-motivated primary care practices along with routine access to bone densitometry.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Morin SM, Djekic-Ivankovic M, Funnell L, Chepesiuk R, Giangregorio L, Braganca Rodrigues I, Ridout R, FeldmanS, Kim S, McDonald-Blumer H, Kline GA, Ward WE, Santesso N, Leslie WD. Patient Engagement in Clinical Guidelines Development: Input from > 1000 Members of the Canadian Osteoporosis Patient Network (Osteoporosis Int 2019) - screening to detect high fracture risk was highly valued by patient stakeholders. Current Canadian practice may reflect the DXA-BMD screening recommendations of the 2010 Guidelines - DXA use already widely practiced and acceptable to physicians and patients. Acceptability to government payers not known; some provinces have recently moved to place restrictions on DXA-BMD use.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	No specific Canadian data	

○ Yes ○ Varies ○ Don't know	Some concerns raised by primary care that it may be to ask family doctors to calculate FRAX scores as a first step screening method prior to deciding upon DXA-BMD

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

We suggest not to implement a population-based screening strategy to identify postmenopausal females and males with clinical risk factors for BMD testing

Current evidence does not support a benefit to **population-wide** screening by offer-to-screen with 1 or 2 step approaches to find individuals at high risk of fracture. **Rather a targeted strategy, is preferred.**

Justification

There is very low certainty of benefit to offering screening to women < 65 years of age on the risk of hip or clinical fracture
Offering screening to women older than 65 years may make a very small difference in the number of hip fractures occuring in the screened population
Offering screening to women older than 65 years likely makes little or no difference in the number of clinical fractures that occur

Subgroup considerations

The identification, assessment and treatment of postmenopausal women who have already sustained a clinical fracture is a separate issue from population screening for primary prevention

Implementation considerations

Monitoring and evaluation

QUESTION 1. B, C, D FRACTURE RISK TRESHOLDS FOR INITIATING PHARMACOTHERAPY

QUESTION 1B: SHOULD TREATMENT OF HIGH FRACTURE RISK VS. ANOTHER CRITERION BE USED FOR INITIATING PHARMACOTHERAPY TO PREVENT THE MOST OSTEOPOROTIC FRACTURES?

QUESTION 1C: SHOULD A SPECIFIC FRACTURE RISK THRESHOLD VS. BMD T-SCORE BE USED FOR INITIATING PHARMACOTHERAPY TO PREVENT THE MOST OSTEOPOROTIC FRACTURES?

QUESTION 1D: SHOULD TREATMENT OF HIGHER RISK SUBGROUPS VS. LOWER RISK SUBGROUPS BE USED FOR INITIATING PHARMACOTHERAPY TO PREVENT THE MOST OSTEOPOROTIC FRACTURES?

Should a specific fracture risk threshold vs. BMD T-score be used for initiating pharmacotherapy to prevent the most osteoporotic fractures?	
POPULATION:	initiating pharmacotherapy to prevent the most osteoporotic fractures
INTERVENTION:	a specific fracture risk threshold
COMPARISON:	BMD T-score
MAIN OUTCOMES:	Hip fractures, osteoporotic T-score, age > 65; Hip fractures, MOF >= 20%, age > 65; Hip fractures, MOF >= 15%, age > 65; All fractures, osteoporotic T-score, age > 65; All fractures, MOF >= 20%, age > 65; All fractures, MOF >= 15%, age > 65; Hip fractures, osteoporotic T-score, age < 65; Hip fractures, MOF >= 20%, age < 65; Hip fractures, MOF >= 15%, age < 65; All fractures, osteoporotic T-score, age < 65; All fractures, MOF >= 20%, age < 65; All fractures, MOF >= 15%, age < 65; Overall ranking across 19 performance metrics;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	One of the central issues, and that with the greatest public health implications, is the recommendation regarding who should be considered for anti-fracture drug therapy. Population models of resource consumption vs proportions of patients under treatment vs expected numbers of fracture prevented are needed in order to assess the potential population impact of any one particular case-finding strategy, prior to making a recommendation.	

○ Varies ○ Don't know	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	We used data from multiple sources to answer FRA Questions 1 B-C-D Also see Q1 Pharmacotherapy group for data supporting treatment threshold for final recommendation	

RCTs:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Incident fractures - pivotal trials data follow-up: mean 3 years	95907 (24 RCTs)	⨁⨁⨁⨁ High	New vertebral fracture by femur neck T-score: • OR 0.51 T<-2.5 vs 0.56 T>-2.5 (both P<0.05) • p-interaction 0.006 • New hip fracture by femur neck T-score: • HR 0.67 T<-2.5 vs 0.72 T>-2.5 (both P<0.05) • p-interaction 0.79 •

			New non-spine fracture by femur neck T-score: • HR 0.81 T<-2.5 vs HR 0.86 T>-2.5 (both P<0.05) • p-interaction 0.08 [1]
Incident fractures - systematic review of RCTs	70623 (143 RCTs)	⨁⨁⨁⨁ High	Meta-regression: • New vertebral fracture: Antiresorptive treatment (BP, SERM and DMAB) is more efficient compared to placebo (RR=0.59, 95% CI: 0.51, 0.69), with improved efficacy following increasing age (p=0.009) but was not affected by other baseline covariates: fracture history p=0.64, lumbar spine T-score p=0.14, BMI p=0.21. • New non-vertberal fracture: Regardless of the baseline covariates (fracture history, age, lumbar spine T-score and BMI) there was an effect of antiresorptive treatment compared to placebo (RR= 0.82, 95% CI: 0.76, 0.89), and was not affected by fracture history p=0.08, age, p=0.12 lumbar spine T-score p=0.63, BMI p=0.45. • New vertebral fracture, new non-vertebral fracture: Compared to either placebo or BP, anabolic treatment (PTHR, romosozumab) reduced risk irrespective of any of the baseline covariates (fracture history, age, lumbar spine T-score and BMI, all p>0.1). • **"Antiresorptive and anabolic treatment were beneficial in fracture risk reduction among postmenopausal women mostly independently of baseline risk"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** [2]
Incident fractures - romosozumab follow-up: mean 1	7163 (1 RCT)	⨁⨁⨁⨁ High[a]	Significant interactions were observed: • Between efficacy and baseline FRAX® probability for composite outcomes of clinical fractures, osteoporotic fractures, and MOF (p = 0.064–0.084), but not vertebral fractures (p > 0.3). • Exclusion of vertebral fractures from each composite fracture outcome (i.e. only nonvertebral fractures included) showed even stronger interactions with baseline FRAX® probability (p = 0.036–0.046). • **"Efficacy of romosozumab on clinical fracture, osteoporotic fracture, and MOF is significantly greater in patients at high baseline fracture risk compared with placebo"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** [3]
Incident fractures - strontium ranelate follow-up: mean 4.6 years	6374 (2 RCTs)	⨁⨁◯◯ Low[a,b]	• The incidence of clinical osteoporotic fractures (vertebral fractures excluded) and morphometric vertebral fractures increased with increasing baseline fracture probabilities. • Treatment with strontiumranelate was associated with a 31% (95% CI=20–39%) decrease in osteoporotic clinical fractures and a 40% decrease in vertebral fractures (95% CI=31–48%)

			• HRs for the effect of strontium ranelate on fracture did not change significantly with increasing fracture probability. • **"Overall, the efficacy of strontium ranelate was not dependent of the levelof fracture risk assessed by FRAX"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .**
Incident fractures - teriparatide follow-up: median 21 months	1637 (1 RCT)	⨁⨁⨁◯ Moderate[a]	• Teriparatide was associated with a 37 % decrease in all nonvertebral fractures (95 % CI 10–56 %) and a 56 % decrease in low-energy non-vertebral fractures (95 % CI 24–75 %) compared with placebo. The risk of morphometric vertebral fractures decreased significantly by 66 % (95 % CI 50–77 %). • HRs did not change significantly with increasing fracture probability (p>0.30). Similar findings when BMD was excluded from the FRAX model, or for hip fracture probability. • **"teriparatide significantly decreases the risk of non-vertebral and morphometric vertebral fractures in women by a similar extent, irrespective of baseline fracture probability"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 4
Incident fractures - raloxifene follow-up: mean 3 years	7703 (1 RCT)	⨁⨁⨁◯ Moderate[a]	• Incidence of clinical fractures and vertebral fractures increased with increasing baseline FRAX probabilities. • Treatment with raloxifene was associated with an 18% decrease in all clinical fractures compared to placebo treatment (HR=0.82; 95% CI=0.71–0.95; p=0.0063) and a 42% decrease in incident morphometric vertebral fractures (HR=0.58; 95% CI=0.48–0.69; pb0.001). • The interaction between fracture probability and treatment was not significant. • **"Overall, there was no significant interaction between efficacy and fracture probability"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 5,6
Incident fractures - SCOOP Management of Patients With High Baseline Hip Fracture Risk by FRAX follow-up: mean 5	12483 (1 RCT)	⨁⨁⨁⨁ High[a]	• Screening led to a 28% reduction in hip fractures over 5 years. No evidence of an effect or interaction was observed for the outcomes of any fracture or osteoporotic fracture. • In those at highest hip fracture risk, the effect on hip fracture increased with baseline FRAX hip fracture probability (p=0.021 for interaction). • **"We conclude that women at high risk of hip fracture based on FRAX probability are responsive to appropriate osteoporosis management"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 7

	Incident fractures - clodronate follow-up: mean 3 years	3974 (1 RCT)	⨁⨁⨁◯ Moderate[a,b]	• The interaction between fractureprobability and treatment efficacy was significant whenprobability was assessed without BMD (p=0.043), but not when BMD was included (p=0.10). • Efficacy was moreevident in those deemed at highest risk. • **"The estimation of an individual's 10-yearprobability of fracture by the FRAX® algorithm identifies patients at high risk of fracture who will respond to bisphosphonate therapy"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 8
	Incident fractures - denosumab follow-up: mean 3 years	7808 (1 RCT)	⨁⨁⨁⨁ High[a]	• Treatment with denosumab over 3 years was associated with a 32% (95% confidence interval [CI] 20% to 42%) decrease in clinical osteoporotic fractures. • Denosumab reduced fracture risk to a greater extent in those at moderate to high risk. • The reduction in fracture was independent of prior fracture, parental history of hip fracture, or secondarycauses of osteoporosis. A low body mass index (BMI) was associated with greater efficacy. • **"Overall, the efficacy of denosumab was greater in those at moderate to highrisk of fracture as assessed by FRAX"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 9
	Incident fractures - bazedoxifene follow-up: mean 3 years	5643 (1 RCT)	⨁⨁⨁◯ Moderate[a,b]	• Bazedoxifene was associated with a significant 39% decrease in incident morphometricvertebral fractures (hazard ratio HR= 0.61; 95% CI= 0.43–0.86;p= 0.005) and a non-statistically significant16% decrease in all clinical fractures (hazard ratio HR= 0.84; 95% CI= 0.67–1.06;p= 0.14) compared to placebo. • HRs for the effect of bazedoxifene on all clinical fractures decreased with increasing fractureprobability but was NS (p-interaction >0.3). • HRs for the effect of bazedoxifene on morphometric vertebralfractures also decreased with increasing fracture probability but was NS (p-interaction >0.3). • **"Bazedoxifene significantly decreased the risk of all clinical fractures and morphometric vertebral fractures in women at or above a FRAX®based fracture probability threshold. These results, consistent with the previous subgroup analysis, suggest that bazedoxifene should be targeted preferentially to women at high fracture risk"** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 10,6
	Incident fractures - abaloparatide follow-up: mean 3 years	1645 (1 RCT)	⨁⨁◯◯ Low[a,b]	• Treatment with abaloparatide-SC was associated with a 69% (95% confidence interval [CI] 38–85%) decrease in major osteoporotic fracture (MOF) and a 43% (95% CI 9–64%) decrease in any clinical fracture compared with placebo. • For all outcomes,HRs tended to decrease (ie, greater efficacy) with increasing fracture probability but was NS (P>0.11). • **"Efficacy of abaloparatide-SC to decrease the risk of major osteoporotic fracture or any clinical fracture in postmenopausal women with low BMD and/or prior fracture appears independent of baseline fracture probability"**

			• **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 11
Incident fractures - alendronate follow-up: mean 3 years	6459 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	• The absolute benefit of alendronate was greatest among women with highest FRAX scores. Results were similar for clinical fractures, major osteoporotic fractures, and radiographic vertebral fractures and whether or not FRAX scores included FN BMD. • **"These results suggest that the effect of alendronate on a relative scale does not vary by FRAX score. "** • **Supports treating those at high risk , with larger absolute benefit expected for those at higher baseline fracture risk .** 12

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a. Limited power to detect or exclude interactions with baseline risk

b. Not available in Canada

Observational studies

One study that comparatively modeled different fracture risk assessment strategies including variations in potential treatment thresholds based on predicted risk (Canada).

The current analysis was performed to inform the following key question as part of the Osteoporosis Canada's Osteoporosis Guideline Update: "*What is the best strategy to identify those at high fracture risk for pharmacotherapy in order to prevent the most fractures, considering both population and patient perspectives?*" These two perspectives were included to balance optimizing societal benefits (population perspective- reduce over-treatment) and efficiently targeting resources towards those at highest risk (patient perspective).

Using the Manitoba BMD Database (**females** 50 years +, n = 66, 878), 65, 115 subjects' data was used in a multi-model simulation with primary outcome of non-traumatic fractures between 6 months and 5 years post baseline assessment. Models were compared to a "treat all" or "treat none" approach representing the two extremes of care.

Using the different strategies, the authors estimated the proportion of individuals getting a fracture risk assessment would ultimately qualify for treatment.

Among those treated for 5 years, the RRR in fractures was estimated according to 2 potential impacts:

1. All therapies result in a 25% relative risk reduction
2. All therapies' benefit varies according to baseline risk (greater RRR for those at higher absolute baseline risk)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BMD T-score	Risk difference with a specific fracture risk threshold
Hip fractures, osteoporotic T-score, age > 65 follow-up: mean 4.4 years	24658 (1 observational study)	⨁⨁◯◯ Low	**RR 0.71** (0.00 to 0.00)	Study population	
				29 per 1,000	**8 fewer per 1,000** (29 fewer to 29 fewer)
Hip fractures, MOF >= 20%, age > 65 follow-up: mean 4.4 years	12048 (1 observational study)	⨁⨁⨁⨁ High	**RR 0.7** (0.0 to 0.0)	Study population	
				52 per 1,000	**15 fewer per 1,000** (52 fewer to 52 fewer)
Hip fractures, MOF >= 15%, age > 65 follow-up: mean 4.4 years	23228 (1 observational study)	⨁⨁⨁◯ Moderate	**RR 0.71** (0.00 to 0.00)	Study population	
				36 per 1,000	**11 fewer per 1,000** (36 fewer to 36 fewer)
All fractures, osteoporotic T-score, age > 65 follow-up: mean 4.4 years	24658 (1 observational study)	⨁⨁◯◯ Low	**RR 0.73** (0.00 to 0.00)	Study population	
				112 per 1,000	**30 fewer per 1,000** (112 fewer to 112 fewer)
				Study population	

All fractures, MOF >= 20%, age > 65 follow-up: mean 4.4 years	12048 (1 observational study)	⨁⨁⨁⨁ High	**RR 0.7** (0.0 to 0.0)	160 per 1,000	**48 fewer per 1,000** (160 fewer to 160 fewer)
All fractures, MOF >= 15%, age > 65 follow-up: mean 4.4 years	12674 (1 observational study)	⨁⨁⨁◯ Moderate	**RR 0.72** (0.00 to 0.00)	Study population	
				127 per 1,000	**35 fewer per 1,000** (127 fewer to 127 fewer)
Hip fractures, osteoporotic T-score, age < 65 follow-up: mean 4.6 years	9668 (1 observational study)	⨁⨁◯◯ Low	**RR 0.78** (0.00 to 0.00)	Study population	
				6 per 1,000	**1 fewer per 1,000** (6 fewer to 6 fewer)
Hip fractures, MOF >= 20%, age < 65 follow-up: mean 4.6 years	431.5 (1 observational study)	⨁⨁◯◯ Low	**RR 0.74** (0.00 to 0.00)	Study population	
				12 per 1,000	**3 fewer per 1,000** (12 fewer to 12 fewer)
Hip fractures, MOF >= 15%, age < 65 follow-up: mean 4.6 years	2524 (1 observational study)	⨁⨁◯◯ Low	**RR 0.74** (0.00 to 0.00)	Study population	
				11 per 1,000	**3 fewer per 1,000** (11 fewer to 11 fewer)
All fractures, osteoporotic T-score, age < 65 follow-up: mean 4.4 years	9668 (1 observational study)	⨁⨁◯◯ Low	**RR 0.8** (0.0 to 0.0)	Study population	
				61 per 1,000	**12 fewer per 1,000** (61 fewer to 61 fewer)
All fractures, MOF >= 20%, age < 65 follow-up: mean 4.6 years	856 (1 observational study)	⨁⨁◯◯ Low	**RR 0.71** (0.00 to 0.00)	Study population	
				93 per 1,000	**27 fewer per 1,000** (93 fewer to 93 fewer)
All fractures, MOF >= 15%, age < 65 follow-up: mean 4.6 years	2524 (1 observational study)	⨁⨁⨁◯ Moderate	**RR 0.74** (0.00 to 0.00)	Study population	
				85 per 1,000	**22 fewer per 1,000** (85 fewer to 85 fewer)
Overall ranking across 19 performance metrics follow-up: mean 4.5 years	66878 (1 observational study)	⨁⨁⨁◯ Moderate	-	INTERVENTION STRATEGY* Age 50-64, Overall ranking (Higher is Better): • T-score only (minimum femur neck, total hip, lumbar) 7.9 • **FRAX with BMD MOF >= 15% 9.3** • FRAX with BMD MOF >= 20% 8.9 Age 65+, Overall ranking (Higher is Better): • T-score only (minimum femur neck, total hip, lumbar) 8.1 • FRAX with BMD MOF >= 15% 9.7	

				• **FRAX with BMD MOF >= 20% 10.5** All ages, Overall ranking (Higher is Better): • T-score only (minimum femur neck, total hip, lumbar) 8.0 • FRAX with BMD MOF >= 15% 9.5 • **FRAX with BMD MOF >= 20% 9.7** *Selected strategies, see reference for all strategies [1]

1. William D. Leslie, Suzanne N. Morin,Lisa M. Lix,Neil Binkley. Comparison of treatment strategies and thresholds for optimizing fracture prevention in Canada: a simulation analysis. Arch Osteoporos; 2020.

Fracture risk and NNT

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
New osteoporotic fracture follow-up: median 8 years	39475 (1 observational study)	⨁⨁◯◯ Low[a,b]	Number needed to treat, NNT, for 3 years to prevent one osteporotic fracture (RRR 0.33), lower is better: • High-risk fracture: 32 • FRAX MOF-BMD>=20%: 33 • VFA positive for vertebral fracture: 34 • FRAX MOF-BMD 10-19%, osteoporotic T-score: 53 • FRAX MOF-BMD <10%, osteoporotic T-score: 79 • FRAX MOF-BMD <20%, not osteoporotic T-score: 93 [1]
New hip fracture follow-up: median 8 years	39475 (1 observational study)	⨁⨁⨁◯ Moderate[a,b]	Number needed to treat, NNT, for 3 years to prevent one hip fracture (RRR 0.4), lower is better: • High-risk fracture: 63 • FRAX MOF-BMD>=20%: 54 • VFA positive for vertebral fracture: 140

			• FRAX MOF-BMD 10-19%, osteoporotic T-score: 113 • FRAX MOF-BMD <10%, osteoporotic T-score: 409 • FRAX MOF-BMD <20%, not osteoporotic T-score: 209 [1]
New clinical vertebral fracture follow-up: median 8 years	39475 (1 observational study)	⨁⨁⨁◯ Moderate[a,b]	Number needed to treat, NNT, for 3 years to prevent one clinical vertebral fracture (RRR 0.5), lower is better: • High-risk fracture: 58 • FRAX MOF-BMD>=20%: 78 • VFA positive for vertebral fracture: 67 • FRAX MOF-BMD 10-19%, osteoporotic T-score: 124 • FRAX MOF-BMD <10%, osteoporotic T-score: 163 • FRAX MOF-BMD <20%, not osteoporotic T-score: 294 [1]

1. William D. Leslie, Suzanne N. Morin,Lisa M. Lix,Neil Binkley. Osteoporosis treatment considerations based upon fracture history, fracture risk assessment, vertebral fracture assessment, and bone density in Canada. Archives of Osteoporosis; 2020.

a. Baseline fracture rates were from a large Canadian clinical registry cohort; fractures prevented from treatment were estimated using relative risks (RR) from a recent large network meta-analysis (107 trials).
b. Women referred for BMD testing are likely to be at higher risk than the general population

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	see above	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Low to high- see above There is less evidence in males	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or	see above	

variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Probably favors the intervention to favors the intervention depending on the intervention threshold	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	no formal cost analysis performed. However, there are cost-effectiveness analyses that demonstrate benefits treating with pharmacotherapy females and males 50 y+ with generic bisphosphonates costs determined by BMD testing and according to the treatment drug offered with high variation (negligible cost - oral bisphosphonates, to high cost - anabolics)	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Evidence from simulation study rated down Evidence from RCTs found to be moderate to high Costs of various anti-fracture medications well known CIHI data (2017) only lists bisphosphonates in the top 100 used medications in Canada (of drugs for osteoporosis) where they place #40 in total program spending.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	no cost effectiveness analyses performed. However taken into consideration when developing the recommendation	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact	Reliance on DXA BMD could increase health inequity in some parts of the nation where DXA is less available.	

○ Probably increased ○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes Patient partners find this strategy to be acceptable. Clearer	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	MOF > 20% as a treatment threshold fits seamlessly into present practice with even more simplicity Previous hip and spine fracture criteria easy to recognize T score based threshold for older individuals will require KT+++	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We **recommend** initiating pharmacotherapy in postmenopausal women and males ≥ 50 years who
a. have had prior hip, vertebra or ≥ 2 fractures *OR*
b. have a 10-year Major Fracture risk ≥ 20% *OR*
c. have a T-score ≤ -2.5 (femoral neck, total hip or lumbar spine) *AND* age ≥70 years.
Strong recommendation: High certainty evidence: a, c ; Moderate certainty evidence: b

We **suggest** initiating pharmacotherapy in postmenopausal women and males ≥ 50 years who
a. have a 10-year Major Fracture risk between 15% and 19.9 % *OR*
b. have a T-score ≤ -2.5 (femoral neck, total hip or lumbar spine) *AND* age < 70 years.

Conditional recommendation: Moderate certainty evidence

Justification

In the absence of an intervention threshold/screening strategy proven to be high-value by prospective RCTs of risk assessment/intervention approach, the setting of a suggested pharmacotherapy intervention threshold will depend upon:
1. Evidence regarding the accuracy of risk assessment models
2. Evidence regarding the efficacy of pharmacotherapy (see pharmacotherapy group questions)
3. Evidence regarding any important interactions with baseline variables and treatment efficacy
4. Evidence regarding the potential population burden of screening and interventions
5. Evidence regarding the expected population fracture outcomes from any given strategy
6. Knowledge of expected costs of any given strategy
7. Consideration of government, physician and patient perspectives

The threshold of MOF > 20% is chosen due to
1. Reasonable accuracy of risk tools to detect MOF risk > 20%
2. One of the top performing strategies in total fractures prevented / persons treated
3. Simplicity, ease of application and similarity to both past Canadian and other international guidelines

4. Potential independence from DXA-BMD where necessary

Subgroup considerations

The evidence in men is of lesser certainty- specifically the simulation study included women only.

Women/men with prevalent or incident low trauma fracture should be considered for pharmacotherapy on the basis of the primary clinical RCT evidence

These recommendations do not apply to special subgroups: glucocorticoid users, secondary osteoporosis etc.

Implementation considerations

KT will be required as these recommendations are new since 2010 Guideline

Monitoring and evaluation

Research priorities

QUESTION 2A: SHOULD DXA SCREENING VS. NO DXA SCREENING BE USED FOR IDENTIFYING THOSE QUALIFYING FOR ANTI-FRACTURE THERAPY DUE TO HIGH FRACTURE RISK BASED UPON AGE, FRACTURE RISK SCORE OR ANOTHER CLINICAL SCORE?

QUESTION 2B: SHOULD SHORTER INTERVAL VS. LONGER INTERVAL FRACTURE RISK RE-ASSESSMENT BE USED FOR CASE-FINDING IN THOSE WHO ARE NOT INITIALLY TREATMENT CANDIDATES?

A. Should DXA screening vs. no DXA screening be used for identifying those qualifying for anti-fracture therapy due to high fracture risk based upon age, fracture risk score or another clinical score? **B. Should shorter interval vs. longer interval fracture risk re-assessment be used for case-finding in those who are not initially treatment candidates?**	
POPULATION:	case-finding
INTERVENTION:	
COMPARISON:	
MAIN OUTCOMES:	
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Screening is important to patient, clinicians and governments Many strategies have been used for the purpose of identifying individuals at high risk for fractures. including age alone, FRAX, BMD-DXA and other tools (OSIRIS and OST) Another important question is the interval at which a BMD test should be repeated in those who do not initiate pharmacotherapy	

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o Trivial
o Small
● Moderate
o Large
o Varies
o Don't know

We aimed to answer these **2** questions

- Should DXA screening vs. no DXA screening be used for identifying those qualifying for anti-fracture therapy due to high fracture risk based upon age, fracture risk score or another clinical score?
- Should shorter interval vs. longer interval fracture risk re-assessment be used for case-finding in those who did not initiate pharmacotherapy?

Observational data from Canadian population based registry were used for these questions
BMD DXA screening versus other strategies (in females and males >50 y; N=28,906; median age 66 y)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Identifying qualification for Treatment Approach 1: prior high-risk fracture, high fracture probability (FRAX-MOF with BMD > 20%), or vertebral fracture on VFA	28906 (1 observational study)	⨁⨁⨁◯ Moderate[a]	Candidate screening tools: • FRAX-MOF without BMD (cutoffs ≥10%, ≥ 15%, ≥ 20%), age alone (cutoffs ≥65 years, ≥75 years); weight alone (cutoffs <57 kg, <70 kg); Simple Calculated Osteoporosis Risk Estimation (SCORE; cutoff ≥6); Osteoporosis Risk Assessment Instrument (ORAI; cutoffs ≥9, ≥17); Study of Osteoporosis Fractures—Study Utilizing Risk Factors (SOFSURF; cutoff >3); Osteoporosis Index of Risk (OSIRIS; cutoffs ≤1, ≤−3); Age, Body Size, No Estrogen (ABONE; cutoff ≥2); Osteoporosis Self-assessment Tool (OST; cutoffs <2, <0, <−3). • FRAX-MOF without BMD: best ability to identify those satisfying Treatment Approach 1 (AUC 0.863 overall, 0.910 women ≥65 years) and was significantly better than all other screening tools (P<0.001). • FRAX-MOF without BMD ≥10%: overall sensitivity 88.7% (99.1% for women ≥65 years) [1]
Identifying qualification for Treatment Approach 2: Above or an osteoporotic BMD T score	28906 (1 observational study)	⨁⨁⨁◯ Moderate[a]	Candidate screening tools: as above: • FRAX-MOF without BMD: best ability to identify those satisfying Treatment Approach 2 (AUC 0.735 overall, 0.770 women ≥65 years) and was significantly better than most other screening tools (P<0.05) except OSIRIS (AUC 0.752 overall , 0.783 women ≥65 years) • FRAX-MOF without BMD ≥10%: overall sensitivity 68.7% (84.2% for women ≥65 years) [1]
Identifying Incident MOF	28906 (1	⨁⨁⨁◯ Moderate[a]	Candidate screening tools: as above:

	observational study)		• FRAX-MOF without BMD: best ability to identify those with incident fracture (AUC 0.652 overall, 0.694 women ≥65 years) and was significantly better than most other screening tools (P<0.05) • FRAX-MOF without BMD ≥10%: overall sensitivity 66.8% (85.2% for women ≥65 years) [1]
Identifying high fracture probability (FRAX-MOF with BMD >= 20%) in women age 50+	50700 (1 observational study)	⨁⨁⨁◯ Moderate[a]	• MOF-clinical >= 10% had 99.3% sensitivity to identify women qualifying for treatment • An age-based rule ("BMD testing is indicated at age 70 if no additional FRAX clinical risk factors are present, or at age 65 if one or more clinical risk factors exists") gave 99,9% sensitivity [2]
Identifying high fracture probability (FRAX-MOF with BMD >= 20%) in men age 50+	4152 (1 observational study)	⨁⨁◯◯ Low[a]	• MOF-clinical >= 10% had 99.1% sensitivity to identify men qualifying for treatment • An age-based rule ("BMD testing is indicated at age 70 if no additional FRAX clinical risk factors are present, or at age 65 if one or more clinical risk factors exists") gave >99,9% sensitivity

1. W.D. Leslie, L.M. Lix N. Binkley. Comparison of screening tools for optimizing fracture prevention in Canada. Archives of Osteoporosis; 2020.
2. W.D. Leslie, S.N. Morin,L.M. Lix N. Binkley. Targeted bone density testing for optimizing fracture prevention in Canada. Osteoporosis International; 2020.

a. Higher risk individuals more likely to be referred for DXA

Age at which FRAX MOF clinical (without BMD) reaches 10%

Women:
NO CRFs: 70 years (IQR 69-72)
1 or more CRFs: 65 years (IQR 62-67)
2 or more CRFs: 59years (IQR56-62)

Men
NO CRFs: 83 years (IQR 82-86)
1 or more CRFs: 76 years (IQR 70-78)
2 or more CRFs: 68years (IQR 65-72)

Shorter interval vs. longer interval fracture risk re-assessment

Leslie et al.
JCEM 2015;100:679
Manitoba registry, women >50 years, n=542 with 3 BMD, untreated
3 fem BMD measures 3 years apart
Correlation of bone loss between 2 time intervals separating 3 BMD measures weak.
Poor correlations between BMD changes in individual patients likely due to large individual measurement errors.

In another study:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Reassessment intervals for transition of 10% of the population from low (<20%) to high (>=20%) major osteoporotic fracture risk follow-up: mean 5.2 years	10564 (1 observational study)	⨁⨁⨁◯ Moderate[a]	Time to reach treatment threshold (95% CI) • Baseline risk <5%: >15 years (14.6 to >15) • Baseline risk 5-9%: 11.4 years (10.3 to 12.3) • Baseline risk 10-14%: 4.9 years (4.7 to 5.4) • Baseline risk 15-19%: 3.1 years (2.9 to 3.3) • New clinical risk factors was associated with shorter interval to reach high fracture risk (see article for details). [1]

1. Leslie, William,D., Morin, Suzanne,N., Lix, Lisa,M., Martineau, Patrick, Bryanton, Mark, McCloskey, Eugene,V., Johansson, Helena, Harvey, Nicholas,C., Kanis, John,A.. Reassessment Intervals for Transition From Low to High Fracture Risk Among Adults Older Than 50 Years. JAMA Network Open; 2020.

a. Women referred for BMD testing are likely to be at higher risk than the general population

•The rate of increase in FRAX-BMD MOF risk is gradual, average doubling-time >15 years without and 8.2 years with new clinical risk factors
•The repeat DXA interval should be longer when fracture risk is low, and shorter when fracture risk is approaching the treatment threshold

Table 2. Time in years (95% confidence interval) for 10% of the population to reach high fracture risk according to fraction of treatment threshold at baseline and change in number of clinical risk factors (CRFs).

	Fixed MOF threshold 20%			
Change in CRFs	<25% threshold = <5% MOF	25-49% threshold = 5-9% MOF	50-74% threshold = 10-14% MOF	75-99% threshold = 15-19% MOF
Decrease	>15 (>15, >15)	>15 (14.5, >15)	8.6 (6.7, 13)	4.1 (3.6, 5.5)
No change	>15 (>15, >15)	>15 (>15, >15)	7.1 (6.5, 8.1)	2.9 (2.9, 3.2)
Increase	13.3 (11.9, 14.6)	7.1 (6.6, 7.7)	3.5 (3.3, 3.7)	2.9 (2.8, 3.2)
Overall	>15 (14.6, >15)	11.4 (10.3, 12.3)	4.9 (4.7, 5.4)	3.1 (2.9, 3.3)

>15 indicates that less than 10% of the population reached high fracture risk by 15 years.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	see above	

Certainty of evidence

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Observational data. However reports from other countries have yielded consistent results No direct evidence	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No direct research evidence; COPN data suggests patients value screening for fracture risk assessment	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	See above "Favors the intervention" implies that there should be guidance given on balancing the desire to repeatedly screen with the desire to detect therapy candidates

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence Assuming base case of yearly FRA, assessment at longer intervals would be expected to moderately reduce resource requirements. Possible large reduction in resource requirements if base case FRA includes BMD every 1-2 years	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	No direct evidence No cost analyses

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No direct evidence No model evidence Existing health database models for less frequent FRA are based on minimum intervals to detect the first 10% of treatment-eligible women (sensitive) Ultimate cost-effectiveness will depend upon agents used, efficacy of agents at baseline risk	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased	No direct evidence Assuming base case of DXA-driven FRA every 1-2 years, a risk score -driven FRA at less frequent intervals would be expected to improve health equity by virtue of less resource requirements	

○ Increased ○ Varies ○ Don't know	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest offering BMD (as a screening strategy) testing to postmenopausal females and males who
a. ≥50 years with a prior fracture or >1 clinical risk factors *OR*
b. ≥65 years with one clinical risk factor for fracture OR
c. ≥70 years.
Conditional recommendation Moderate certainty evidence

We suggest that for postmenopausal females and males who do not meet the threshold for pharmacotherapy or chose not to initiate therapy, BMD testing can be repeated at:
5-10 years if the risk of major fracture is <10%;
5 years if the risk of major fracture is 10–15%;
3 years if the risk of major fracture is greater than 15%.

Conditional recommendation Low certainty evidence

A shorter re-testing interval may be considered for those with new clinical risk factors

Justification

1. Repeat BMD measures at 2 to 5 year intervals will detect the majority of women who are reaching a T < -2.5 threshold; However, this is only relevant within a BMD-only treatment paradigm.
2. There is no clear clinical value to repeat BMD measures within 3 to 5 years for the purpose of updating FRA according to the new BMD or BMD change since previous
3. In women aged < 65 without major fracture risk factors or prevalent OP fracture, BMD measures rarely identify individuals who warrant OP treatment using the current threshold (MOF20%)
4. In women older than 65 years who do not already qualify for OP treatment or FRAX-based BMD testing (10% FRAX-MOF), repeat FRA at 5 to 7 year intervals reliably detects the first 10% of ageing women to become treatment *candidates if not otherwise acquiring new fracture risk factors.*
5. In women older than 65 who do not already qualify for OP treatment or FRAX-based BMD testing (10% FRAX-MOF) but who acquire one or more new fracture risk factors, repeat FRA at 3 to 5 year intervals reliably detects the first 10% of such women to become treatment candidates.

Subgroup considerations

Post-menopausal females and males who sustain a fragility fracture should be assessed with BMD to further define fracture risk

There are less data in males – the certainty of the evidence was rated down.

Implementation considerations

Monitoring and evaluation

Research priorities

QUESTION 2C: FRAX VS. CAROC

SHOULD WOMEN (MEN) AGED 50 YEARS OR OLDER UNDERGO DXA SCREENING (VERSUS NO SCREENING) BASED UPON AGE, OST, FRACTURE RISK SCORE WITHOUT DXA, OR PRIOR FRACTURE TO IDENTIFY THOSE AT HIGH RISK FOR FUTURE FRACTURES FOR WHOM ANTI-FRACTURE THERAPY HAS BEEN SHOWN TO BE EFFECTIVE?

Should FRAX vs. CAROC be used for accurately predict fracture outcomes?	
POPULATION:	accurately predict fracture outcomes
INTERVENTION:	FRAX
COMPARISON:	CAROC
MAIN OUTCOMES:	MOF_Mod; MOF_High; MOF_Low;
SETTING:	in women (men) age 50 years or older
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	The WHO fracture risk assessment (FRAX) and Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tools can both be used to determine an individual's 10-year risk of osteoporotic fracture. However, these tools differ in their risk calculation. Overall, observed fracture rates for Canadians are in close agreement with the rates predicted by both tools. In 2010, Osteoporosis Canada recommended the CAROC or FRAX tool be adopted for fracture prevention	

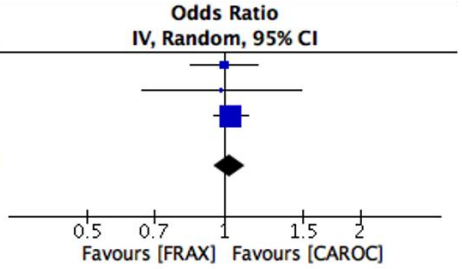
Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	• **Observed 10-year fracture risk agreed with the expected risk for each risk category using CAROC or FRAX (low, moderate or high)** • **In cases of discordances between FRAX and CAROC, FRAX was favoured in almost all cases (only one discordance favoured CAROC)**	

Study or Subgroup	CAROC Events	CAROC Total	FRAX Events	FRAX Total	Weight	Odds Ratio IV, Random, 95% CI
Leslie 2011_Camos_Low	274	4486	281	4607	20.7%	1.00 [0.84, 1.19]
Leslie 2011_Man_Low	48	731	53	797	3.7%	0.99 [0.66, 1.48]
Leslie 2016_Low	965	15079	1076	17362	75.6%	1.03 [0.95, 1.13]
Total (95% CI)		**20296**		**22766**	**100.0%**	**1.03 [0.95, 1.11]**
Total events	1287		1410			

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)



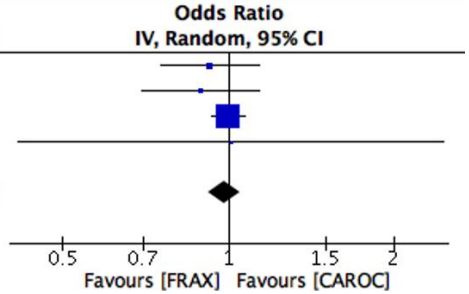
MOF (Moderate Risk)

•Moderate fracture risk 10-20%

•CAROC (13.7%) and FRAX (13.9%)

Study or Subgroup	CAROC Events	CAROC Total	FRAX Events	FRAX Total	Weight	Odds Ratio IV, Random, 95% CI
Leslie 2011_Camos_Mod	209	1546	225	1559	10.5%	0.93 [0.76, 1.14]
Leslie 2011_Man_Mod	137	937	162	1005	7.1%	0.89 [0.70, 1.14]
Leslie 2016_Mod	1781	12909	1611	11674	81.9%	1.00 [0.93, 1.07]
Roux 2014_Mod	9	152	12	205	0.5%	1.01 [0.42, 2.47]
Total (95% CI)		**15544**		**14443**	**100.0%**	**0.98 [0.92, 1.05]**
Total events	2136		2010			

Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 3 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)



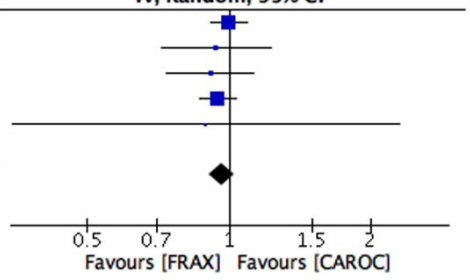
Results: MOF (High Risk)

•High fracture risk > 20%

•CAROC (18.4%) and FRAX (18.5%)

Study or Subgroup	CAROC Events	CAROC Total	FRAX Events	FRAX Total	Weight	Odds Ratio IV, Random, 95% CI
Crandall 2019_High	1034	7926	1034	7926	41.0%	1.00 [0.91, 1.10]
Leslie 2011_Camos_High	148	665	124	531	4.7%	0.94 [0.72, 1.23]
Leslie 2011_Man_High	255	875	230	741	7.7%	0.91 [0.74, 1.13]
Leslie 2016_High	1445	6072	1246	5024	46.2%	0.95 [0.87, 1.03]
Roux 2014_High	11	148	8	97	0.4%	0.89 [0.35, 2.31]
Total (95% CI)		**15686**		**14319**	**100.0%**	**0.97 [0.91, 1.02]**
Total events	2893		2642			

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)



Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
MOF_High							
3	observational studies	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate
MOF_Mod							
3	observational studies	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate
MOF_Low							
2	observational studies	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate

Predicted CAROC	Predicted Canadian FRAX		
Leslie 2011 Camos Cohort (N=6, 682) Ns with discordance and observed fracture %			
	FRAX Low (<10%)	FRAX Moderate (10-20 %)	FRAX High (>20%)
CAROC Low (<10 %)		191 **(10.9%)**	0
CAROC Moderate (10-20 %)	312 **(9.2%)**		65 **(19.9%)**
CAROC High (>20%)	0	199 **(18.4%)**	
Leslie 2016** Manitoba Cohort (N= 34,060): N with discordance and observed fracture %			
CAROC Low (<10 %)		1512 **(10.2%)**	0
CAROC Moderate (10-20 %)	1669 **(7.5%)**		840 **(20.4%)**
CAROC High (>20%)	0	1135 **(15.9%)**	

- only one discordance favoured CAROC;
- all other discordances favoured FRAX

** Leslie 2016: risk of competing mortality taken in consideration

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	There was no undesirable effect reported.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ● Moderate ○ High ○ No included studies	

Outcomes	With CAROC	With FRAX	Difference	Relative effect (95% CI)
MOF_High	247 per 1,000	**224 per 1,000** (210 to 239)	**23 fewer per 1,000** (37 fewer to 8 fewer)	**OR 0.88** (0.81 to 0.96)
MOF_Mod	137 per 1,000	**126 per 1,000** (119 to 135)	**11 fewer per 1,000** (18 fewer to 2 fewer)	**OR 0.91** (0.85 to 0.98)
MOF_Low	60 per 1,000	**59 per 1,000** (55 to 64)	**1 fewer per 1,000** (5 fewer to 4 more)	**OR 0.98** (0.91 to 1.07)

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes were MOF. Fracture prediction is highly valued by patients and clinicians	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Both FRAX and CAROC predict fracture well. The undesirable effect is low. The balance of effects slightly favors FRAX. Furthermore, there will be a new version of FRAX (including falls, number of fractures, etc) that will be made available in the next 2 years. This will further Enhance its predictive ability. CAROC will not be updated.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost of using FRAX and CAROC is similar. Although one must obtain the data and there are more data to obtain when using FRAX. Depending who will obtain the data, costs may be more important when using FRAX. On the other hand, FRAX can be sued without BMD input- and then becomes less expensive than CAROC FRAX is a multiattribute aggregate score designed to calculate the 10-year probability of hip and major osteoporotic fracture for individuals between the ages of 40 to 90. The following indicators are used in its calculation: age, sex, height, weight, previous fragility fracture, parental hip fracture history, current smoking status, current use of glucocorticoids, diagnosis of rheumatoid arthritis (RA), alcohol intake (3 or more units daily), diagnosis of secondary osteoporosis, and femoral neck bone mineral density (BMD) T score. The Canadian FRAX tool has been shown to predict observed fracture rates in large-scale Canadian population-based and cohort studies. The CAROC tool (developed based on FRAX)uses data on sex, age, and femoral neck BMD T scores to estimate the semiquantitative risk for a major osteoporotic fracture within the next 10 years in 3 categories: low (< 10%), moderate (10%-20%), and high (> 20%). Two special circumstances also lead individuals to be "bumped" up to the next categorization of risk in the CAROC system — the presence of fragility fractures or prolonged corticosteroid use. Persons with one of these risk factors would move from either low risk to moderate risk or from moderate risk to high risk. In CAROC, when both factors are present, the patient is considered to be at high fracture risk.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ● High ○ No included studies	The resources needed and cost of using FRAX and CAROC are comparable. The resources including DXA to estimate BMD are widely available. **HOWEVER, with the development of FRAXplus which will incorporate new variables such as falls, site of fracture, number of fractures; CAROC will become less accurate than FRAXplus. There will not be an updated CAROC tool.**	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably	Using FRAX or CAROC would have a limited impact on health equity, seeing that both tools are mostly used with BMD input	

no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	In a study conducted by Beattie et al. (2014), it was shown that family physicians prefer FRAX report over CAROC (1). In an opinion paper by Hammond et al. (2017), Imaging physicians (radiologists and nuclear medicine specialists) believe that the CAROC tool is the more practical fracture risk assessment tool for imaging physicians reporting DXA scans. Imaging physicians usually have sufficient knowledge of the patient's medical history to permit accurate entry of some of the important variables required by the FRAX tool. Also, the relative ease of use of CAROC is a valuable asset in most BMD settings. However, imaging physicians acknowledge the international status of FRAX and its value to experts in bone health, who, in specialist settings, are in the best position to apply the important clinical judgement required to advise preventive or therapeutic intervention (2). 1- Beattie KA, Ioannidis G, MacDermid JC, Grewal R, Papaioannou A, Adachi JD, Hodsman AB. Appropriate osteoporosis treatment by family physicians in response to FRAX vs CAROC reporting: results from a randomized controlled trial. Journal of Clinical Densitometry. 2014 Oct 1;17(4):458-65. 2- Hammond I, Burrell S, Lyons DJ, Lentle BC. FRAX vs CAROC for the Canadian imaging physician: an existential dilemma. Canadian Association of Radiologists Journal. 2017 Nov;68(4):445-6.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	It was shown that FRAX and CAROC are feasible fracture prediction tools (1,2). 1- Beattie KA, Ioannidis G, MacDermid JC, Grewal R, Papaioannou A, Adachi JD, Hodsman AB. Appropriate osteoporosis treatment by family physicians in response to FRAX vs CAROC reporting: results from a randomized controlled trial. Journal of Clinical Densitometry. 2014 Oct 1;17(4):458-65. 2- Hammond I, Burrell S, Lyons DJ, Lentle BC. FRAX vs CAROC for the Canadian imaging physician: an existential dilemma. Canadian Association of Radiologists Journal. 2017 Nov;68(4):445-6.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	**Probably no**	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

For all people with osteoporosis, we suggest using FRAX as a fracture prediction tool. CAROC is also an acceptable fracture prediction tool (Conditional recommendation; moderate-certainty evidence).

Justification

- In the three fracture risk categories (low, moderate and high), there are no differences in the observed MOF between CAROC and FRAX.
- Observed 10-year fracture risk agreed with the expected risk for each risk category using CAROC or FRAX.
- In cases of discordances between FRAX and CAROC, it mostly favours FRAX.
- Based on the current literature, CAROC and FRAX are comparable in the accuracy of predicting fracture risk in the Canadian population.
- Publication of FRAXplus will limit the use of CAROC

Subgroup considerations

No subgroup Consideration

Implementation considerations

It is important to include Stakeholders (such as patients, family physicians, and imaging physicians) in the implementation strategy.

Monitoring and evaluation

Not applicable

Research priorities

More rigorous RCT comparing the fracture prediction accuracy of FRAX versus CAROC are required.

QUESTION 3: SHOULD WOMEN (MEN) AGED 50 YEARS OR OLDER WITHOUT KNOWN VERTEBRAL FRACTURES RECEIVE VERTEBRAL IMAGING ASSESSMENT (VFA) OR SPINE X-RAYS (VERSUS NO SPINE IMAGING) TO FIND THOSE WITH VERTEBRAL FRACTURES FOR WHOM ANTI-FRACTURE THERAPY MAY BE GIVEN?

Should vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays vs. no vertebral imaging or no VF found on imaging be used for finding those with vertebral fractures for whom anti-fracture therapy may be given to reduce future fractures??	
POPULATION:	finding those with vertebral fractures for whom anti-fracture therapy may be given to reduce future fractures?
INTERVENTION:	vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays
COMPARISON:	no vertebral imaging or no VF found on imaging
MAIN OUTCOMES:	3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (< 3 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (3-4.9 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (5-10 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (>10 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean <3 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean 3-4.9 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean 5-10 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean >10 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean <3 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean 3-4.9 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean 5-10 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (>10 year follow-up); 3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident VFs (over 10 years), modelling study; 3b. Does vertebral imaging vs no imaging (or no VF found on imaging) lead to increased use of anti-fracture treatment?; 3c. Vertebral imaging vs no imaging (or no VF found on imaging) for reduced risk of fracture due to a change in treatment; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident vertebral fractures, age; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, BMD; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fracture, BMD; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident vertebral fractures, BMD; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, women; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, men; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fractures, women; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fractures, men; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, women; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, women; 3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, men;
SETTING:	General population (men/women 50 years or older) without known vertebral fractures (VFs)
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The purpose was to determine whether the recommendations for screening of vertebral fractures (VF) in the updated clinical practice guidelines for the diagnosis and management of osteoporosis should be revised from the previous iteration, in which those at moderate fracture risk based on CAROC criteria were recommended to consider thoracolumbar radiography to assess for silent VF. With the 2010 OC guideline recommendation, it is not clear to family physicians and osteoporosis specialists whether all moderate risk patients should be *screened* for silent VF with thoracolumbar radiography; and if not, who should be screened. This is an important problem because: · Two-thirds of vertebral fractures are silent · Vertebral fractures predict important future clinical fractures · Identification of vertebral fractures on vertebral imaging leads to increased use of anti-fracture therapy · Anti-fracture treatment reduces fracture risk in those with vertebral fractures · Thus screening for vertebral fractures in at risk men and women will prevent fractures. This review assessed the impact of imaging for prevalent VF (using VFA or spine x-rays) in individuals over the age of 50 to determine associations with incident fractures and the initiation of osteoporosis medications. Data on various subgroups (age, BMD, glucocorticoid use, height loss, self reported VF) were also assessed to determine yield of screening as well as the incidence of subsequent fractures and treatment initiation in these particular subgroups. Leading international osteoporosis organizations (i.e., National Osteoporosis Foundation, International Society for Clinical Densitometry and Osteoporosis International) have recommended screening for silent VFs based on using clinical indicators to help select at-risk patients for thoracolumbar radiographic assessment (or VFA – where available). However, disagreements exist between which clinical indicators were proposed by these organizations, and further examination is needed to determine which clinical indicators apply the best to Canadian patients.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Should women / men aged 50 years and older without known vertebral fractures (VFs) receive vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays (versus no vertebral imaging) to find those with vertebral fractures for whom anti-fracture therapy may be given to prevent fractures? **Data Table pertaining to the following sub-questions:** *3a. Does vertebral imaging predict clinically important fractures?* *3b. Does vertebral imaging lead to increased use of anti-fracture treatment?* *3c. Does vertebral imaging lead to reduced risk of fracture due to a change in treatment?* *3d. For which subgroup(s) does vertebral imaging have the largest effect on treatment? i.e. are there subgroups within the population that particularly benefit from vertebral imaging?*	

Outcomes	With no vertebral imaging or no VF found on imaging	With vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays	Difference	Relative effect (95% CI)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (< 3 year follow-up)	20 per 1,000	**42 per 1,000** (30 to 58)	**22 more per 1,000** (10 more to 39 more)	**HR 2.13** (1.51 to 3.02)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (3-4.9 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 2.08** (0.98 to 4.43)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (5-10 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 2.00** (1.36 to 2.94)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (>10 year follow-up)	0 per 1,000	**NaN per 1,000** (NaN to NaN)	**-- per 1,000** (-- to --)	**HR 1.49** (1.24 to 1.80)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean <3 year follow-up)	Not enough data to pool estimates. **Study 1:** 71/1004 (7.1%) with pVF had incident fx, 118/2734 (4.3%) without pVF had incident fx; RR (95% CI): 1.03 (0.68-1.56); **Study 2**: 154/1575 (9.8%) with pVF had incident fx, 398/8397 without pVF had incident fx (4.7%), HR (95% CI) 2.13 (1.51, 3.02)			
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean 3-4.9 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.67** (1.28 to 2.28)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean 5-10 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.84** (1.39 to 2.42)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean >10 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.73** (1.38 to 2.16)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean <3 year follow-up)	Not enough data to pool estimates. **Study 1**: OR (95% CI)= 2.80 (1.90-4.13); **Study 2:** HR (95% CI)= 3.09 (1.85, 5.16). Total number of patients with VF = 3274, Total number of pts without pVF = 9375.			
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 4.00** (3.56 to 4.50)

important fractures: All vertebral fractures (mean 3-4.9 year follow-up)					
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean 5-10 year follow-up)	38 per 1,000	**125 per 1,000** (87 to 176)	**87 more per 1,000** (49 more to 138 more)	**OR 3.63** (2.43 to 5.44)	
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (>10 year follow-up)	163 per 1,000	**408 per 1,000** (349 to 469)	**245 more per 1,000** (186 more to 306 more)	**OR 3.54** (2.75 to 4.54)	
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident VFs (over 10 years), modelling study	For women aged 50 and over for a 10-year time horizon, the new VF incidence was 54.6% for No screening, and 23.3% for Do screening with a two-year interval. For men aged 50and over it was also associated with lower new VF incidence (8.4% for Do screening vs. 22.5% for No screening). The incidence of new VFs was reduced in all screening strategies compared to no screening: 29.4% forwomen and 12.5% for men in both X-ray following the VFA and VFA only strategies and 35% for women and 17.5% for men in the X-ray only strategy. The new VF prevention effect was greater in women, andmore prominent in older people (women ≥ 70, men ≥ 80) than people ≥ 50 years. The preventive effect of Do screening onnew VFs was 41.0% for women ≥ 70 and 32.8% for men ≥ 80 compared with No screening.				
3b. Does vertebral imaging vs no imaging (or no VF found on imaging) lead to increased use of anti-fracture treatment?	*4% to 124% increase in prescription of osteoporosis medications based on VFA/spinal radiographs. *OR (95% CI) 2.24 (1.16, 4.33) at 6 months; 0.99 (0.45–2.23) for at 6-12 months for prescription of OP medications in screening (high risk group, given radiographs) vs control group (no screening or radiograph) *OR (95% CI) = 3.2 (2.1,5.1) & 2.77 (2.40, 3.19) for being prescribed new fracture prevention medication in those with positive VFA compared to those negative for VFA				
3c. Vertebral imaging vs no imaging (or no VF found on imaging) for reduced risk of fracture due to a change in treatment	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable	
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident vertebral fractures, age	• Cauley 2007: < 70 yrs, OR (95% CI): 3.56 (2.53-5.03) > 70 yrs, OR (95% CI): 2.84 (1.92-4.21). • Kadowaki 2010: 50–59, RR (95% CI): 7.19 (1.04–49.6) 60-69, RR (95% CI): 3.19 (1.27–7.97) 70-79, RR (95% CI): 2.34 (1.33–4.11) • Two other studies demonstrated increasing incidence of VF with age, among those with pVF.				
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, BMD	• Increasing odds of incident fx with decreasing BMD + pVF. • Unadjusted OR (95% CI) of incident hip fracture in pts with pVF (Grade 2 or more) compared to no pVF: *T score >= -1: 0.98 (0.05, 17.76), *T score <-1 to >-2.5: 1.52 (0.65,3.57), *T score <= -2.5: 4.61 (1.11, 19.19)				
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fracture, BMD	• Increasing risk of incident fx with decreasing BMD + pVF in three studies. • Risks range from T-score >=-1.0 with prevalent VF = 1.7, without pVF - 1.0 to T-score -4 with pVF= 6.4%, without pVF = no pVF =3.8%. • Pongchaiyakul 2005: * T score >= −2.5, HR (95% CI): 6.7 (1.5–29.1) (for incident vertebral fractures), * T score >= −2.5, HR (95% CI): 3.2 (95% CI, 1.2–8.7) (for any fx), Osteopenia and normal BMD, HR (95% CI): 7.0 (2.3,18.1) (for incident symptomatic vertebral fractures). • Prince 2018: T score >= -1, OR (95% CI): 1.06 (0.22, 5.06), >* T score <-1 to >-2.5, OR (95% CI): 2.00 (1.05, 3.83), * T score <= -2.5, OR (95% CI): 2.55 (0.59, 10.95)				
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident vertebral fractures, BMD	• Increasing risk of incident fracture with decreasing BMD + prevalent VF in three studies. • Kim 2011: * T-score −1.0 to −2.5, OR (95% CI)= 6.5 (2.09–19.90),* T-score ≤−2.5, OR (95% CI) = 3.7 (1.66–8.48). • Cauley 2007: *Women with prevalent VF + BMD in osteoporotic range: absolute risk of vertebral fractures > 50% * Women with normal BMD and no prevalent fracture: absolute risk = 9%. * Interaction between BMD and prevalent vertebral fracture was not statistically significant				
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.70** (1.37 to 2.10)	

3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, men	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 2.05** (1.49 to 2.82)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.53** (1.37 to 1.70)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fractures, men	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.74** (1.30 to 2.33)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 3.86** (3.20 to 4.67)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**OR 3.35** (2.74 to 4.10)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, men	From three studies: • RR: 2.2 (0.9-5.0) • OR: 6.65 (1.47-30.03) • OR: 4.42 (3.10-6.29). • Total pts in VF group = 564, total pts in non-VF group = 6896			

Note:
There is one modelling study assessing the incidence of vertebral fractures among those screened with x-ray following VFA, only VFA, only X-ray, and no screening in South Korea (Oh 2018). A Markov model was developed using administrative data of individuals over the age of 50 years. Otherwise, studies compared those who had a prevalent VF vs. those who did not have a prevalent VF on vertebral imaging.

Data from the Osteoporosis Canada Guidelines on Screening for Vertebral Fractures
Question: Should [screening for silent vertebral fracture (VF) by using clinical indicators] vs. [not using clinical indicators] be used in [in men and women] with [moderate risk for fractures] to assess for silent VF using thoracolumbar radiography (or Vertebral Fracture Assessment / VFA, where available).
•Selected clinical indicators: age, BMD, sex, historical height loss, prior fracture, glucocorticoid treatment, self reported VF

Clinical indicator examined in systematic review	Sex	Chance for prevalent VF without clinical indicator / prevalence of VF in moderate fracture risk patients in CAMOS	Chance for prevalent VF with clinical indicator, based on relative effect observed in systematic review	Difference (95% CI)	Relative effect (OR [95% CI]) observed in systematic review	Certainty of evidence in systematic review (GRADE: high, moderate, low, very low)
BMD -2.5 vs. -1.0 **Tscore (desired: FN, evaluated: FN < hip < LS)**	*Women*	150 per 1000	300 per 1000 (270 to 345)	150 more per 1000 (from 120 to 195 more)	2.0 (1.8 - 2.3)	HIGH
	Men	240 per 1000	504 per 1000 (384 to 672)	264 more per 1000 (from 144 more to 432 more)	2.1 (1.6 - 2.8)	HIGH
age 65 vs. 50 years	*Women*	150 per 1000	375 per 1000 (300 to 465)	225 more per 1000 (from 150 more to 315 more)	2.5 (2.0 - 3.1)	HIGH
	Men	240 per 1000	360 per 1000 (288 to 432)	120 more per 1000 (from 48 more to 192 more)	1.5 (1.2 - 1.8)	HIGH
historical height loss 6 vs. 0 cm (evaluated: historical, desired: prospective)	*Women*	150 per 1000	300 per 1000 (270 to 345)	150 more per 1000 (from 120 to 195 more)	2.0 (1.8 - 2.3)	MODERATE
	Men	240 per 1000	432 per 1000 (336 to 576)	192 more per 1000 (from 96 more to 336 more)	1.8 (1.4 - 2.4)	LOW
prior fracture (evaluated: any definition, desired: peripheral fragility fracture after 40)	*Women*	150 per 1000	300 per 1000 (225 to 405)	150 more per 1000 (from 75 more to 255 more)	2.0 (1.5 - 2.7)	MODERATE
	Men	240 per 1000	384 per 1000 (312 to 456)	144 more per 1000 (from 72 more to 216 more)	1.6 (1.3 - 1.9)	MODERATE
glucocorticoid treatment (evaluated: any definition, desired: ≥3 consecutive months at ≥5 mg/d)	*Women*	150 per 1000	225 per 1000 (150 to 345)	75 more per 1000 (from 0 more to 195 more)	1.5 (1.0 - 2.3)	LOW
	Men	240 per 1000	264 per 1000 (120 to 624)	24 more per 1000 (from 120 less to 384 more)	1.1 (0.5 - 2.6)	LOW
self-reported VF (evaluated: un/documented, desired: undocumented)	*Women*	150 per 1000	-	-	21 (10-45)	VERY LOW
	Men	240 per 1000	na	na	na	na

Data from CaMOS cohort: Prevalent moderate-to-severe VF *in CAROC moderate-risk patients* that would be selected or not selected for screening based on different clinical indicators

Clinical indicators	WOMEN									MEN									
	No. moderate-risk patients selected		No. moderate-risk patients *not* selected		A % selected for screening	B % with VF detected among selected	C % with VF detected among moderate risk with VF	D % with VF detected among all moderate risk	E % with VF missed among all moderate risk	No. moderate-risk patients selected		No. moderate-risk patients *not* selected		A % selected	C % with VF detected among selected	B % with VF detected among moderate risk with VF	E % with VF detected among all moderate risk	D % with VF missed among all moderate risk
	(+) VF	(-) VF	(+) VF	(-) VF						(+) VF	(-) VF	(+) VF	(-) VF					
All (moderate risk)	158	918	0	0	100	15	100	15	0	28	88	0	0	100	24	100	24	0
Age																		
≥65	137	763	21	155	84	15	87	13	2	21	61	7	27	71	26	75	18	6
≥65 or HHL ≥6cm	140	772	18	146	85	15	89	13	2	22	64	6	24	74	26	79	19	5
BMD																		
Op fn	39	213	119	705	23	15	25	4	11	6	17	22	71	20	26	21	5	19
Op fn or HHL ≥6cm	87	336	71	582	39	21	55	8	7	14	27	14	61	35	34	50	12	12
Op fn/ls	69	336	89	582	38	17	44	6	8	7	19	21	69	22	27	25	6	18
Op fn/ls or HHL ≥6cm	105	444	53	474	51	19	66	10	5	15	27	13	61	36	36	54	13	11
Age + BMD																		
≥65 + Op fn	32	153	126	765	17	17	20	3	12	6	14	22	74	17	30	21	5	19
≥65 + Op fn or HHL ≥6cm	82	279	76	639	34	23	52	8	7	14	24	14	64	33	37	50	12	12
≥65 + Op fn/ls	57	265	101	653	30	18	36	5	9	7	16	21	72	20	30	25	6	18
≥65 + Op fn/ls or HHL ≥6cm	96	378	62	540	44	20	61	9	6	15	24	13	64	34	38	54	13	11
Add glucocorticoids (GC) or fragility fracture after age 40 (FFx)																		
≥65 + Op fn or HHL ≥6cm or GC	82	297	76	621	35	22	52	8	7	17	34	11	54	44	33	61	15	9
≥65 + Op fn or HHL ≥6cm or FFx	101	408	57	510	47	20	64	9	5	23	65	5	23	76	26	82	20	4
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65 + Op fn/ls or HHL ≥6cm or FFx	115	499	43	419	57	19	73	11	4	24	65	4	23	77	27	86	21	3

Undesirable effects include:

1. Additional radiation exposure due to imaging for prevalent VFs. VFA has a radiation dose of 2-50 µSv while spine x-rays have a radiation dose of 600 µSv. As a comparison, a chest x-ray is 0.02 mSV (or 20000 µSv) and annual background radiation is 1-5 mSV..

2. Extra testing may also contribute to patient anxiety and inconvenience. This however would be mitigated by the use of VFA (where available) since it can be performed at the same time as DXA and only takes a few additional minutes.

3. Misclassification of prevalent VFs, which could lead to unnecessary treatment:

A) False positives

* Those that are not VF but other type of deformities: to minimize, recommend diagnosis of VF based on moderate-to severe grades (not mild).
* Those that are not low-trauma but high-trauma VF or due to specific transient conditions: to minimize, recommend obtaining clinical history / biomechanics to help determine cause.
* Those that happened before age 40: to minimize, recommend obtaining clinical history to help determine age when fractured.

B) False negatives: This may be less of a problem than false positive. False negatives can occur in the acute setting with a new fracture, but usually those progress over time.

4) Training is required for the reading of spine Xrays and VFA in determining what is a vertebral fracture and what is not.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Should women / men aged 50 years and older without known vertebral fractures (VFs) receive vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays (versus no vertebral imaging) to find those with vertebral fractures for whom anti-fracture therapy may be given to prevent fractures?

Data Table pertaining to the following sub-questions:
3a. Does vertebral imaging predict clinically important fractures?
3b. Does vertebral imaging lead to increased use of anti-fracture treatment?
3c. Does vertebral imaging lead to reduced risk of fracture due to a change in treatment?
3d. For which subgroup(s) does vertebral imaging have the largest effect on treatment? i.e. are there subgroups within the population that particularly benefit from vertebral imaging?

Outcomes	With no vertebral imaging or no VF found on imaging	With vertebral imaging with vertebral fracture assessment (VFA) or spine x-rays	Difference	Relative effect (95% CI)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (< 3 year follow-up)	20 per 1,000	**42 per 1,000** (30 to 58)	**22 more per 1,000** (10 more to 39 more)	**HR 2.13** (1.51 to 3.02)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (3-4.9 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 2.08** (0.98 to 4.43)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (5-10 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 2.00** (1.36 to 2.94)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident hip fractures (>10 year follow-up)	0 per 1,000	**NaN per 1,000** (NaN to NaN)	**-- per 1,000** (-- to --)	**HR 1.49** (1.24 to 1.80)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean <3 year follow-up)	Not enough data to pool estimates. **Study 1:** 71/1004 (7.1%) with pVF had incident fx, 118/2734 (4.3%) without pVF had incident fx; RR (95% CI): 1.03 (0.68-1.56); **Study 2**: 154/1575 (9.8%) with pVF had incident fx, 398/8397 without pVF had incident fx (4.7%), HR (95% CI) 2.13 (1.51, 3.02)			
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean 3-4.9 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.67** (1.28 to 2.28)

3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean 5-10 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.84** (1.39 to 2.42)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident clinical fragility fractures (mean >10 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.73** (1.38 to 2.16)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean <3 year follow-up)	Not enough data to pool estimates. **Study 1**: OR (95% CI)= 2.80 (1.90-4.13); **Study 2:** HR (95% CI)= 3.09 (1.85, 5.16). Total number of patients with VF = 3274, Total number of pts without pVF = 9375.			
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean 3-4.9 year follow-up)	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 4.00** (3.56 to 4.50)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (mean 5-10 year follow-up)	38 per 1,000	**125 per 1,000** (87 to 176)	**87 more per 1,000** (49 more to 138 more)	**OR 3.63** (2.43 to 5.44)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: All vertebral fractures (>10 year follow-up)	163 per 1,000	**408 per 1,000** (349 to 469)	**245 more per 1,000** (186 more to 306 more)	**OR 3.54** (2.75 to 4.54)
3a. Vertebral imaging vs no imaging (or no VF found on imaging) for predicting clinically important fractures: Incident VFs (over 10 years), modelling study	For women aged 50 and over for a 10-year time horizon, the new VF incidence was 54.6% for No screening, and 23.3% for Do screening with a two-year interval. For men aged 50and over it was also associated with lower new VF incidence (8.4% for Do screening vs. 22.5% for No screening). The incidence of new VFs was reduced in all screening strategies compared to no screening: 29.4% forwomen and 12.5% for men in both X-ray following the VFA and VFA only strategies and 35% for women and 17.5% for men in the X-ray only strategy. The new VF prevention effect was greater in women, andmore prominent in older people (women ≥ 70, men ≥ 80) than people ≥ 50 years. The preventive effect of Do screening onnew VFs was 41.0% for women ≥ 70 and 32.8% for men ≥ 80 compared with No screening.			
3b. Does vertebral imaging vs no imaging (or no VF found on imaging) lead to increased use of anti-fracture treatment?	*4% to 124% increase in prescription of osteoporosis medications based on VFA/spinal radiographs. *OR (95% CI) 2.24 (1.16, 4.33) at 6 months; 0.99 (0.45–2.23) for at 6-12 months for prescription of OP medications in screening (high risk group, given radiographs) vs control group (no screening or radiograph) *OR (95% CI) = 3.2 (2.1,5.1) & 2.77 (2.40, 3.19) for being prescribed new fracture prevention medication in those with positive VFA compared to those negative for VFA			
3c. Vertebral imaging vs no imaging (or no VF found on imaging) for reduced risk of fracture due to a change in treatment	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident vertebral fractures, age	• Cauley 2007: < 70 yrs, OR (95% CI): 3.56 (2.53-5.03) > 70 yrs, OR (95% CI): 2.84 (1.92-4.21). • Kadowaki 2010: 50–59, RR (95% CI): 7.19 (1.04–49.6) 60-69, RR (95% CI): 3.19 (1.27–7.97) 70-79, RR (95% CI): 2.34 (1.33–4.11) • Two other studies demonstrated increasing incidence of VF with age, among those with pVF.			
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging)	• Increasing odds of incident fx with decreasing BMD + pVF. • Unadjusted OR (95% CI) of incident hip fracture in pts with pVF (Grade 2 or more) compared to no pVF: *T score >= -1: 0.98 (0.05, 17.76), *T score <-1 to >-2.5: 1.52 (0.65,3.57), *T score <= -2.5: 4.61 (1.11, 19.19)			

have the largest effect on treatment: Incident hip fractures, BMD				
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fracture, BMD	• Increasing risk of incident fx with decreasing BMD + pVF in three studies. • Risks range from T-score >=-1.0 with prevalent VF = 1.7, without pVF - 1.0 to T-score -4 with pVF= 6.4%, without pVF = no pVF =3.8%. • Pongchaiyakul 2005: * T score >= −2.5, HR (95% CI): 6.7 (1.5–29.1) (for incident vertebral fractures), * T score >= −2.5, HR (95% CI): 3.2 (95% CI, 1.2–8.7) (for any fx), Osteopenia and normal BMD, HR (95% CI): 7.0 (2.3,18.1) (for incident symptomatic vertebral fractures). • Prince 2018: T score >= -1, OR (95% CI): 1.06 (0.22, 5.06), >* T score <-1 to >-2.5, OR (95% CI): 2.00 (1.05, 3.83), * T score <= -2.5, OR (95% CI): 2.55 (0.59, 10.95)			
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident vertebral fractures, BMD	• Increasing risk of incident fracture with decreasing BMD + prevalent VF in three studies. • Kim 2011: * T-score −1.0 to −2.5, OR (95% CI)= 6.5 (2.09–19.90),* T-score ≤−2.5, OR (95% CI) = 3.7 (1.66–8.48). • Cauley 2007: *Women with prevalent VF + BMD in osteoporotic range: absolute risk of vertebral fractures > 50% * Women with normal BMD and no prevalent fracture: absolute risk = 9%. * Interaction between BMD and prevalent vertebral fracture was not statistically significant			
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.70** (1.37 to 2.10)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident hip fractures, men	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 2.05** (1.49 to 2.82)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.53** (1.37 to 1.70)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: Incident clinical fragility fractures, men	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.74** (1.30 to 2.33)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 3.86** (3.20 to 4.67)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, women	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**OR 3.35** (2.74 to 4.10)
3d. For which subgroup does vertebral imaging vs no imaging (or no VF found on imaging) have the largest effect on treatment: All vertebral fractures, men	From three studies: • RR: 2.2 (0.9-5.0) • OR: 6.65 (1.47-30.03) • OR: 4.42 (3.10-6.29). • Total pts in VF group = 564, total pts in non-VF group = 6896			

Note:
There is one modelling study assessing the incidence of vertebral fractures among those screened with x-ray following VFA, only VFA, only X-ray, and no screening in South Korea (Oh 2018). A Markov model was developed using administrative data of individuals over the age of 50 years. Otherwise, studies compared those who had a prevalent VF vs. those who did not have a prevalent VF on vertebral imaging.

Data from the Osteoporosis Canada Guidelines on Screening for Vertebral Fractures

Question: Should [screening for silent vertebral fracture (VF) by using clinical indicators] vs. [not using clinical indicators] be used in [in men and women] with [moderate risk for fractures] to assess for silent VF using thoracolumbar radiography (or Vertebral Fracture Assessment / VFA, where available).

•Selected clinical indicators: age, BMD, sex, historical height loss, prior fracture, glucocorticoid treatment, self reported VF

Clinical indicator examined in systematic review	Sex	Chance for prevalent VF without clinical indicator / prevalence of VF in moderate fracture risk patients in CAMOS	Chance for prevalent VF with clinical indicator, based on relative effect observed in systematic review	Difference (95% CI)	Relative effect (OR [95% CI]) observed in systematic review	Certainty of evidence in systematic review (GRADE: high, moderate, low, very low)
BMD -2.5 vs. -1.0 **Tscore (desired: FN, evaluated: FN < hip < LS)**	*Women*	150 per 1000	300 per 1000 (270 to 345)	150 more per 1000 (from 120 to 195 more)	2.0 (1.8 - 2.3)	HIGH
	Men	240 per 1000	504 per 1000 (384 to 672)	264 more per 1000 (from 144 more to 432 more)	2.1 (1.6 - 2.8)	HIGH
age 65 vs. 50 years	*Women*	150 per 1000	375 per 1000 (300 to 465)	225 more per 1000 (from 150 more to 315 more)	2.5 (2.0 - 3.1)	HIGH
	Men	240 per 1000	360 per 1000 (288 to 432)	120 more per 1000 (from 48 more to 192 more)	1.5 (1.2 - 1.8)	HIGH
historical height loss 6 vs. 0 cm (evaluated: historical, desired: prospective)	*Women*	150 per 1000	300 per 1000 (270 to 345)	150 more per 1000 (from 120 to 195 more)	2.0 (1.8 - 2.3)	MODERATE
	Men	240 per 1000	432 per 1000 (336 to 576)	192 more per 1000 (from 96 more to 336 more)	1.8 (1.4 - 2.4)	LOW
prior fracture (evaluated: any definition, desired: peripheral fragility fracture after 40)	*Women*	150 per 1000	300 per 1000 (225 to 405)	150 more per 1000 (from 75 more to 255 more)	2.0 (1.5 - 2.7)	MODERATE
	Men	240 per 1000	384 per 1000 (312 to 456)	144 more per 1000 (from 72 more to 216 more)	1.6 (1.3 - 1.9)	MODERATE
glucocorticoid treatment (evaluated: any definition, desired: ≥3 consecutive months at ≥5 mg/d)	*Women*	150 per 1000	225 per 1000 (150 to 345)	75 more per 1000 (from 0 more to 195 more)	1.5 (1.0 - 2.3)	LOW
	Men	240 per 1000	264 per 1000 (120 to 624)	24 more per 1000 (from 120 less to 384 more)	1.1 (0.5 - 2.6)	LOW
self-reported VF (evaluated: un/documented, desired: undocumented)	*Women*	150 per 1000	-	-	21 (10-45)	VERY LOW
	Men	240 per 1000	na	na	na	na

Data from CaMOS cohort: Prevalent moderate-to-severe VF *in CAROC moderate-risk patients* that would be selected or not selected for screening based on different clinical indicators

Clinical indicators	WOMEN									MEN									
	No. moderate-risk patients selected		No. moderate-risk patients *not* selected		A % selected for screening	B % with VF detected among selected	C % with VF detected among moderate risk with VF	D % with VF detected among all moderate risk	E % with VF missed among all moderate risk	No. moderate-risk patients selected		No. moderate-risk patients *not* selected		A % selected	C % with VF detected among selected	B % with VF detected among moderate risk with VF	E % with VF detected among all moderate risk	D % with VF missed among all moderate risk
	(+) VF	(-) VF	(+) VF	(-) VF						(+) VF	(-) VF	(+) VF	(-) VF					
All (moderate risk)	158	918	0	0	100	15	100	15	0	28	88	0	0	100	24	100	24	0
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Undesirable effects include:

1. Additional radiation exposure due to imaging for prevalent VFs. VFA has a radiation dose of 2-50 µSv while spine x-rays have a radiation dose of 600 µSv. As a comparison, a chest x-ray is 0.02 mSV (or 20000 µSv) and annual background radiation is 1-5 mSV..

2. Extra testing may also contribute to patient anxiety and inconvenience. This however would be mitigated by the use of VFA (where available) since it can be performed at the same time as DXA and only takes a few additional minutes.

3. Misclassification of prevalent VFs, which could lead to unnecessary treatment:

A) False positives

* Those that are not VF but other type of deformities: to minimize, recommend diagnosis of VF based on moderate-to severe grades (not mild).
* Those that are not low-trauma but high-trauma VF or due to specific transient conditions: to minimize, recommend obtaining clinical history / biomechanics to help determine cause.
* Those that happened before age 40: to minimize, recommend obtaining clinical history to help determine age when fractured.

B) False negatives: This may be less of a problem than false positive. False negatives can occur in the acute setting with a new fracture, but usually those progress over time.

4) Training is required for the reading of spine Xrays and VFA in determining what is a vertebral fracture and what is not.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	· There is no RCT with direct evidence showing that vertebral imaging reduces fractures. However, it is very difficult to conduct an RCT to assess this question -- requires a large sample size and a long duration of followup, expensive. · The inclusion of mostly observational studies downgrades the evidence in GRADE, however observational studies are the best evidence that there is in this area. · There is one RCT where patients were randomized to a screening tool and if the pt screened high risk, then they will obtain a spine radiograph. Control group did not get screening tool or radiographs. This RCT showed increase in medication use and a reduction in fractures. This RCT is of moderate quality. Overall -> moderate certainty	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcomes (in individuals > 50 years old and subgroups of interest: · Incident hip fracture · Incident clinical fragility fracture · Incident vertebral fracture · Initiation of osteoporosis pharmacologic medication there is general agreement regarding the importance of diagnosing prevalent VFs due to the effect is has on risk assessment.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Our systematic review of the literature showed that the desirable effects outweigh the undesirable effects, and favor the intervention in those at risk for vertebral fractures (older age, lower BMD T-score).	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Depending on a province or territory, the cost for thoracolumbar radiographic assessment per person ranges from $20 to $120 CAD. This cost is typically covered by the healthcare system. VFA (by DXA) costs are significantly less than thoracolumbar radiographic assessment ($40-$50 CAD), but is currently only covered by the provincial health plan in the province of Manitoba. VFA is available at other (mainly academic) BMD testing facilities that have purchased specialized software and received necessary training, but not covered by provincial health plan.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Cost-effectiveness of thoracolumbar radiography** to detect silent VF in postmenopausal women was previously examined in a US study (**Schousboe 2005**). · The study found the screening intervention to be cost-effective (assuming a societal willingness to pay per QUALY gained of $50,000) based on ≥10% pre-test probability of having a prevalent VF present. The pre-test probability was based on 2 clinical indicators: age and femoral neck BMD. · Three strategies were compared using a Markov cost-utility model: (1) screening + 5-year ALD therapy for those with ≥1 mild-to-severe VF detected + 5-year extended / initiated ALD therapy following subsequent incident fracture; (2) no screening + 5-year ALD therapy for all + 5-year extended or initiated ALD therapy following subsequent incident fracture; (3) no screening + no initial ALD therapy + 5-year initiated ALD therapy following subsequent incident fracture. These post-screening health states were considered: no incident fracture, incident wrist fracture, incident clinical / radiographic VF, incident hip fracture, incident other fracture, death). A 50% and 30% reduction in VF and non-VF risk due to ALD therapy was considered, respectively. · The assumed direct costs were in USD: Thoracolumbar radiography - $80 per test; ALD therapy - $842 per year; follow-up medical visits - $52 per each year on ALD therapy. The direct medical costs assigned to acute hip, vertebral, wrist, and "other" incident fracture were, respectively: $16116, $6702, $3726, and $5561. **Cost-effectiveness of VFA** has been demonstrated in several studies owing to its high diagnostic yield, low burden to patients, low radiation, low costs ($30-40 USD), and presumable initiation of treatment for patients who would have otherwise been missed, due to the effect of prevalent VFs on risk assessment. Many systematic reviews have demonstrated a reduction of fracture risk and subsequent hospitalizations due to the osteoporosis pharmacologic treatment (Wells 2008). **Schousboe 2006** demonstrated the cost-effectiveness of VFA in postmenopausal US women with T-scores >-2.5. · Three strategies were compared (1) no initial drug therapy, (2) 5 years of initial alendronate therapy, and (3) VFA followed by 5 years of alendronate therapy among those with at least one VF confirmed by radiography (VFA strategy). · *Results for the base-case analyses showed that the cost per quality adjusted life year (QALY) gained for the VFA strategy relative to no initial drug therapy ranged from 18,000 US dollars (for a 60-yr-old with a femoral neck T-score of -2.4) to 77,000 US dollars (for an 80-yr-old with a T-score of -1.5).* · *VFA with selective confirmatory radiography is cost-effective, assuming a societal willingness to pay per QALY gained of 50,000 US dollars, for postmenopausal women aged 60 to 80 yr with femoral neck T-scores between -2.0 and -2.4, and for women age 60 or 70 yr with a T-score of -1.5.* · *Assuming a societal willingness to pay of 100,000 US dollars per QALY gained, VFA is also cost-effective for women age 80 yr with a T-score of -1.5.* ***Vokes 2010*** *assessed a convenience sample of US men and women referred to BMD testing.* · *Assuming a 15% prevalence of vertebral fractures, an RFI>2 (where RFI is a risk factor index incorporating age, T-score, height loss, GC use, non-VF, self-reported VF) had a 24% positive and 97% negative predictive value and required VFA scanning of three women at a cost of $60 (assuming a $20 cost/VFA scan) to detect one with vertebral fracture(s).* · *If all subjects were to have VFA scan, the number needed to scan and cost of VFA scanning (assuming $20/ scan) needed to find one subject with vertebral fracture would be six subjects and $120. Scanning only subjects with RFI ≥2 would decrease these figures by 50% (three subjects and $60)* **Nayak 2016** demonstrated effectiveness of VFA in US men over 50 years old. · An *individual-level state-transition cost-effectiveness model with a lifetime time horizon was used to identify the cost-effectiveness of different osteoporosis screening strategies: (1) (DXA; the Osteoporosis Self-Assessment Tool (OST) & (2) fracture risk assessment strategy using age, femoral neck bone mineral density (BMD), and Vertebral Fracture Assessment (VFA)); screening initiation ages (50, 60, 70, or 80); and repeat screening intervals (5 years or 10 years).* · *In base-case analysis, no screening was a less effective option than all other strategies evaluated.* · *Screening strategies that most frequently appeared as most cost-effective in base-case analysis and one-way sensitivity analyses when assuming willingness-to-pay of $50,000/QALY or $100,000/QALY included screening initiation at age 50 with the fracture risk assessment strategy and repeat screening every 10 years; screening initiation at age 50 with fracture risk assessment and repeat screening every 5 years; and screening initiation at age 50 with DXA and repeat screening every 5 years.* **Oh 2018** *compared screening strategies (using modelling)* **including x-ray following VFA, only VFA, only X-ray, and no screening** *for detecting VF in South Korean individuals over the age of 50 over a 10-year time horizon*. · X-ray following VFA strategy had the lowest cost, followed by the X-ray only, and VFA only strategies (cost = cost of test and VF treatment). · For women, expected costs were €967 higher and for men, expected costs were €631 higher for screening than no screening · X-ray following VFA strategy was less expensive than the others for both women and men. · The second economic option was X-ray only strategy, then VFA only strategy (Incremental cost of €821, €938, and €1142 for women; €477, €515, and €899 for men per capita, respectively). · For older individuals: o The expected costs were €1602 per woman aged 70 and over, and €1429 per man aged 80 and over. · The overall expected cost of X-ray only strategy was the highest in the subgroup for old people whereas the cost of VFA only strategy was the highest in the base case analysis

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	In general, cost-effectiveness studies have favored screening for vertebral fractures.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was found regarding the impact of recommending screening for VF on equity. In Canada, the thoracolumbar radiographic assessment (and VFA assessment – where available) is covered by the healthcare system, providing free access to those who can reach a clinic with the proper facilities. Remote and rural populations may not have equitable access for screening of vertebral fractures. Indirect influence on equity may include having to find extra time and money for travel to a hospital or x-ray lab to undergo thoracolumbar radiographic assessment. However, we don't anticipate any difference in the relative effectiveness of this intervention for disadvantaged subgroups.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Sixty-two participants were recruited from the clinic and 681 completed the survey online (mean age 66 years old (range 40-91 years), 85.3% women). The response rate from clinic and online participants was 100% and 89.7%, respectively. Almost all participants (93.8%) thought it was important to look for silent spinal fractures and almost all (93.5%) reported willingness to have spinal radiographs to look for a hitherto undetected spinal fracture. Willingness was positively related to increasing levels of vertebral fracture risk, willingness to initiate osteoporosis medications, and test accuracy, and was negatively related to additional time requirements required for screening and radiation exposure. Willingness was also related to participants' knowledge, attitudes and beliefs regarding medical care and osteoporosis. The following level of **chance for having a silent VF present** would make this proportion of patients willing to undergo a spine x-ray (n,%): 1 in 100 to 1 in 10 (1% to 10%)**–** 379 **(50.6%)**, 2 in 10 to 4 in 10 (20% to 40%)- 204 **(27.4%)**, 5 in 10 or more (≥50%) – 158 **(21.3%),** missing -5 **(0.7%)**. **Needing to take osteoporosis medication** would make **5.8%** (n=43) of patients less likely to undergo a spine x-ray (**42.8%** more likely (n=318), **45.1%** no influence (n=335) & **6.3%** missing (n=47). **Willingness to start taking osteoporosis medications, if the benefit of reducing risk for future fractures was found to outweigh the risk for experiencing unwanted side effects (n,%):** 43 **(5.8%)** would not be willing, 249 **(33.5%)** would consider it, 386 **(52%)** would be willing, 65 **(8.7%)** did not answer.	

	Research evidence on uptake: A prospective study evaluated a program for screening for silent VF that was running in 15 family practices in the Bristol UK area (Clark et al, 2012, JBMR 27: 664-671). This study observed that out of all participants who were selected for screening (n=401) based on clinical indicators (HHL, n-VF Fx, back pain, rib to pelvis distance) and were invited to undergo a standard thoracolumbar radiograph, **77%** (n=310) had the radiograph while 23% did not undergo the radiograph.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Thoracolumbar radiography is readily available in Canada and can be easily ordered by family physicians or osteoporosis specialist. No research evidence was found about the burden of implementing screening for silent VF to family physicians, osteoporosis specialists or radiologists. Screening for silent VF with VFA has already been implemented and studied as part of fracture liaison services (Bristol, UK; Glasgow UK) and routine BMD testing (Danville, USA). Also, screening for silent VF with thoracolumbar radiography has been implemented and studied in 15 family practices (Bristol, UK). **Finally, screening for silent VF with VFA has been implemented in Canada, in the Manitoba Bone Density Program, and has been running for ~10 years.** Screening and the varying quality of VF assessment may lead to incorrectly classified VFs and further downstream consequences to patients and stakeholders.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest that women/men aged 65 or older AND with T-scores -2.5 and below without known vertebral fractures should receive vertebral imaging with VFA or lateral spine radiographs as part of fracture risk assessment. (conditional recommendation, moderate confidence)

Justification

The overall GRADE judgements supported the development of this recommendation and favoured screening in this patient population. The problem was deemed to be large, with large desirable effects and small undesirable effects associated with screening for vertebral fractures in adults over 50 years old. Moderate certainty of evidence and probably no important uncertainty or variablility in values, coupled with balance of effects and cost-effectiveness favouring the intervention, as well as moderate savings in resources, high certainty of evidence of required resources, no impact on health equity, and the acceptability and feasilibilty of this recommendation also led to the development of this recommendation.

Subgroup considerations

Based on the Canadian Multicentre Osteoporosis Study (CAMOS) data (included above), individuals aged 65 and above with T-scores -2.5 and below appear to have the most benefit from screening.

Implementation considerations

It may be less expensive and easier for health care providers and patients to have vertebral imaging done as part of DXA (for centres that can to do so), rather than having an additional appointment to have a lateral spine radiograph.

Monitoring and evaluation

Close the care gap and try to determine if following this recommendation will effect change in use of medications to reduce fractures.

Research priorities

Research priorities include evidence that the new guideline would indeed reduce fractures.

QUESTION 4A: BONE MINERAL DENSITY

SHOULD POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS OR OLDER RECEIVING TREATMENT TO PREVENT FRACTURES BE MONITORED WITH REPEAT DXA, FRACTURE RISK SCORE WITH DXA (E.G., FRAX, CAROC), BONE TURNOVER MARKERS (BTM) VERSUS CLINICALLY (NO SPECIFIC TESTING)?

Should BMD monitoring vs. no BMD monitoring be used for reduction in fracture outcomes in men and women while on anti-osteoporosis treatment?	
POPULATION:	reduction in fracture outcomes in men and women while on anti-osteoporosis treatment
INTERVENTION:	BMD monitoring
COMPARISON:	no BMD monitoring
MAIN OUTCOMES:	
SETTING:	Summary
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes **Osteoporosis** poses an immense burden to the society in terms of morbidity, mortality and financial **cost**. To reduce this burden, it is essential to accurately assess the individual patient's fracture risk and, where indicated, to initiate appropriate treatment that reduces fracture probability. Current **monitoring** approaches use bone mineral density measurement by Dual Energy X-ray Absorptiometry (DXA). **Monitoring while on therapy** is a very important issue to patients, clinicians and policy makers. Currently most patients receive BMD to monitor response to therapy often with intervals as short as 12 months. In certain provinces, there are recommendations in place regarding monitoring intervals (12, 24 or 36 months). The **2010 Canadian Guidelines**: "For patients who are undergoing treatment, repeat measurement of bone mineral density should initially be performed after one to three years". If bone mineral density has improved or remain unchanged, the patient is considered to have had a good response to therapy." **IOF (2018)** In postmenopausal osteoporosis, treatment induced increments in BMD with inhibitors of bone turnover are modest (typically 2% per year) in comparison to the precision error of repeat measurements (typically 1-2%) so that the time interval of repeat estimates must be sufficiently long in order to determine whether any change is real	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

We did not identify any RCT that evaluated monitoring of BMD on fracture outcomes in patients on antiosteoporosis therapy.
Therefore, the evidence considered for the question on monitoring of BMD in patients while on therapy is presented in answer to 3 sub-questions, relying mostly on **indirect** evidence.

1. *Does monitoring while on therapy lead to a change in fracture outcomes **within a treated** population?*
We found only one observational study using data from the Manitoba BMD Registry linked to provincial administrative healthcare data.
Monitoring interval: mean 3.2 years (SD 0.9);
Outcomes: MOF and Hip fractures over 10 years.
Effect is small to moderate. (see additional considerations)

Question: BMD monitoring compared to no BMD monitoring for reduction in fracture outcomes within a treated population [1]
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD monitoring	no BMD monitoring	Relative (95% CI)	Absolute (95% CI)		
Major osteoporotic fracture (observational study) (follow up: mean 10 years; assessed with: Fracture codes)												
1	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would reduce the demonstrated effect dose response gradient [c]	591/4559 (13.0%)	632/4559 (13.9%)	**HR 0.90** (0.82 to 1.00)	**13 fewer per 1,000** (from 23 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hip fracture (observational study) (follow up: mean 10 years; assessed with: Fracture codes)												
1	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would reduce the demonstrated effect dose response gradient [d]	167/4559 (3.7%)	215/4559 (4.7%)	**HR 0.75** (0.64 to 0.89)	**12 fewer per 1,000** (from 17 fewer to 5 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. Newcastle Ottawa scale> Good quality
b. BMD monitoring is inferred as it is not possible from administrative data to know why MDs decide to repeat or not BMD assessment with DXA.
c. Risk Major osteoporotic fracture in monitored versus non monitored over 10 years: 591/4559 (M) vs 632/4559 (NM)= RR: 0.13/0.14= 0.93 (95% CI 0.84-1.0);; ARR (NM-M) = 0.14-0.13 =0.01 p=0.208; 1.8 MOF/ 1000 person years HR 0.90 95% CI (0.82-1.00) (adjusted analyses)
d. Risk HIP fracture in monitored vs non monitored over 10 years: 167/4559 (M) vs 215/4559 (NM)=RR: 0.04/0.05= 0.78 (95% CI 0.64-0.95)) ARR (NM-M) = 0.05-0.04= 0.01 p=0.012 1.4 HIP / 1000 person years; HR 0.75 95% CI (0.64-0.89) (adjusted analyses)

References

1. Leslie, W.D.,et al.,. Association of Bone Density Monitoring in Routine Clinical Practice With Anti-Osteoporosis Medication Use and Incident Fractures: A Matched Cohort Study.. J Bone Miner Res,; 2019.

2. *Does an observed increase/decrease (vs stability) in the monitoring parameter while **on therapy** predict a difference in **fracture** outcomes within a treated population? (if insufficient data in 4A).*
This is **indirect evidence** as monitoring was not the question of interest in these studies.
We used data from 2 RCT studies evaluating BMD change and fracture outcomes in the **treated** arm of the trials. See table below.
Monitoring interval was 3 years (mean 3.2 y)
The **effect is moderate** depending on the trial and fracture site.

(Of note, other publications were identified, data were presented **as linear regression analyses** with BMD as a continuous variable making it impossible to show the data in GradePro tables.
For example: an increase of BMD of approximately 3 % at 3 years with **alendronate** was associated with a relative reduction of Radiographic VF by 47%. If we use a baseline rate of 15 R VF per 1000 p per year, this would translate in a reduction of 7 RVF per 1000 p-year. *Data not shown*)

Question: BMD change on therapy compared to no BMD change on therapy for predicting fracture outcomes [1234567891011121314151617181920212223242526272829303132 33]
Setting:
Bibliography: [a]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD change on therapy	no BMD change on therapy	Relative (95% CI)	Absolute (95% CI)		
WATTS (2004) VERTEBRAL FRACTURES_ while on treatment (risedronate) lumbar spine BMD Increase (>0%) vs No BMD increase (<0%) (follow up: mean 3 years; assessed with: radiographs)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	9.8/100 (9.8%)	15.5/100 (15.5%)	**RR 0.56** (0.38 to 0.82)	**68 fewer per 1,000** (from 96 fewer to 28 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Jacques 2012 Non vertebral fractures and change in total HIP BMD change while on therapy (follow up: mean 3 years; assessed with: report)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	9.6/100 (9.6%)	7/100 (7.0%)	**OR 0.73** (0.24 to 0.59)	**18 fewer per 1,000** (from 52 fewer to 27 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. only larger RCTs were kept in the analyses (ie placebo groups with at least 50 participants). Most studies identified report positive effects of treatment on BMD
b. indirect evidence because change in BMD while on treatment vs not on treatment (PBO): not our question

We also compiled data from 2 observational studies (using similar population over a different stduy period 9 or 12 years) Data shown here are for the study with timeline of 9 years.
Monitoring interval: mean 4.5 years
Effect was small

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD change on therapy	no BMD change on therapy	Relative (95% CI)	Absolute (95% CI)		
MAJOR OSTEOPOROTIC FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD INCREASE vs no BMD change (follow up: median 9.2 years; assessed with: fracture codes)												
1	observational studies	not serious	not serious	serious [b]	serious [c]	none	234/1995 (11.7%)	446/3333 (13.4%)	**RR 0.86** (0.73 to 1.00) [d]	**19 fewer per 1,000** (from 36 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
MAJOR OSTEOPOROTIC FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD DECREASE VS NO BMD CHANGE (follow up: median 9.2 years)												
1	observational studies	not serious	not serious	not serious	not serious	none	211/1235 (17.1%)	446/3333 (13.4%)	**RR 1.22** (1.03 to 1.43)	**29 more per 1,000** (from 4 more to 58 more)	⨁⨁◯◯ LOW	CRITICAL
HIP FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD INCREASE VS NO BMD CHANGE (follow up: median 9.2 years; assessed with: fracture codes)												
1	observational studies	not serious	not serious	not serious	serious [c]	none	44/1995 (2.2%)	90/3333 (2.7%)	**RR 0.80** (0.56 to 1.15)	**5 fewer per 1,000** (from 12 fewer to 4 more)	⨁◯◯◯ VERY LOW	CRITICAL
HIP FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD decrease vs NO BMD change (follow up: median 9.2 years; assessed with: fracture codes)												
1	observational studies	not serious	not serious	not serious	not serious	none	56/1235 (4.5%)	90/3333 (2.7%)	**RR 1.60** (1.15 to 2.23)	**16 more per 1,000** (from 4 more to 33 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. only larger RCTs were kept in the analyses (ie placebo groups with at least 50 participants). Most studies identified report positive effects of treatment on BMD
b. indirect evidence because change in BMD while on treatment vs not on treatment (PBO): not our question
c. wide CI. crosses null value

Since not many studies evaluated the effectiveness of BMD monitoring strategies, we also have looked at clinical effectiveness evidence that support the change in BMD and fracture outcomes in RCT via meta-regression analysis (change Treatment group – PBO group and Fx risk). We show Bouxsein (2019) meta-regression analysis.

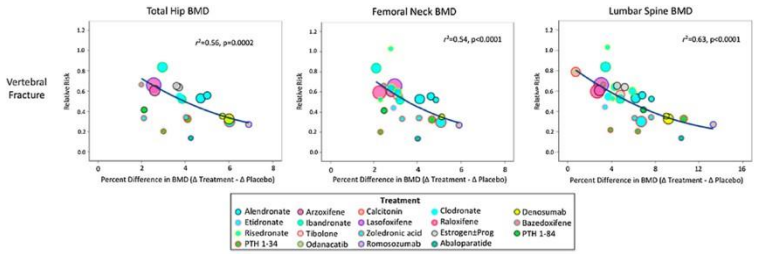


Fig. 1. Association between treatment-related differences in BMD (Active-Placebo, in %) and reduction in vertebral fracture risk. Individual trials are represented by circles with areas that are approximately proportional to the number of fractures in the trial. Drugs of the same class are represented by the symbols of the same color.

Table 5. Estimated Fracture Risk Reduction Associated With BMD Improvement

	Vertebral fracture	Hip fracture	Nonvertebral fracture
Δ Total hip BMD			
2%	28%	16%	10%
4%	51%	29%	16%
6%	66%	40%	21%
Δ Femoral neck BMD			
2%	28%	15%	11%
4%	55%	32%	19%
6%	72%	46%	27%
Δ Lumbar spine BMD			
2%	28%	22%	11%
8%	62%	38%	21%
14%	79%	51%	30%

BMD = bone mineral density.

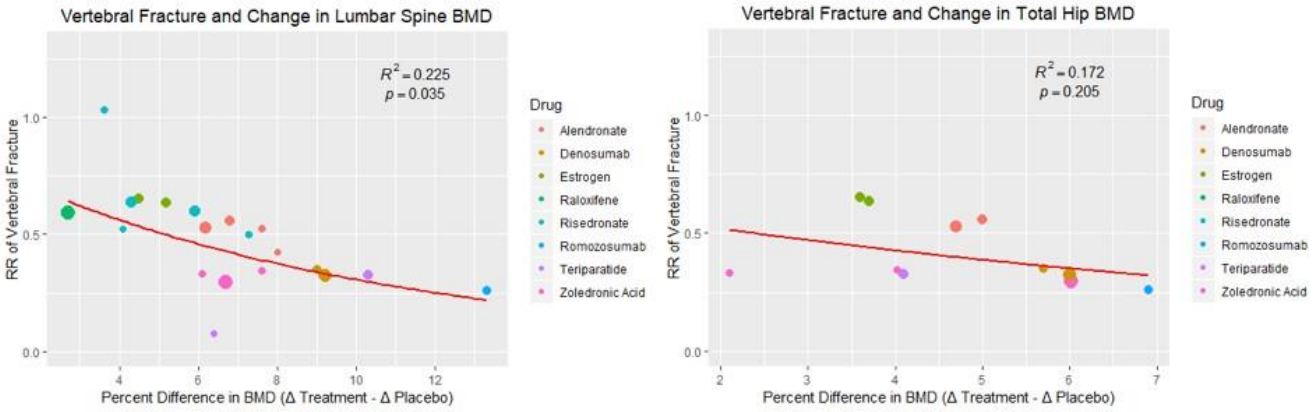
(Bouxsein M and coll. J Bone Miner Res. 2019 Apr;34(4):632-642

We also perform a meta regression using data of medications available in Canada. The results were similar but less robust than those of Bouxsein. Linear models were created to estimate the relationship between mean percentage difference in BMD –lumbar spine and total hip- (active minus placebo group) and the logarithm of the RR for each fracture site.
Again this is **indirect evidence** comparing BMD change in **treated vs non treated (PBO)** participants in large RCTs and fracture outcomes.

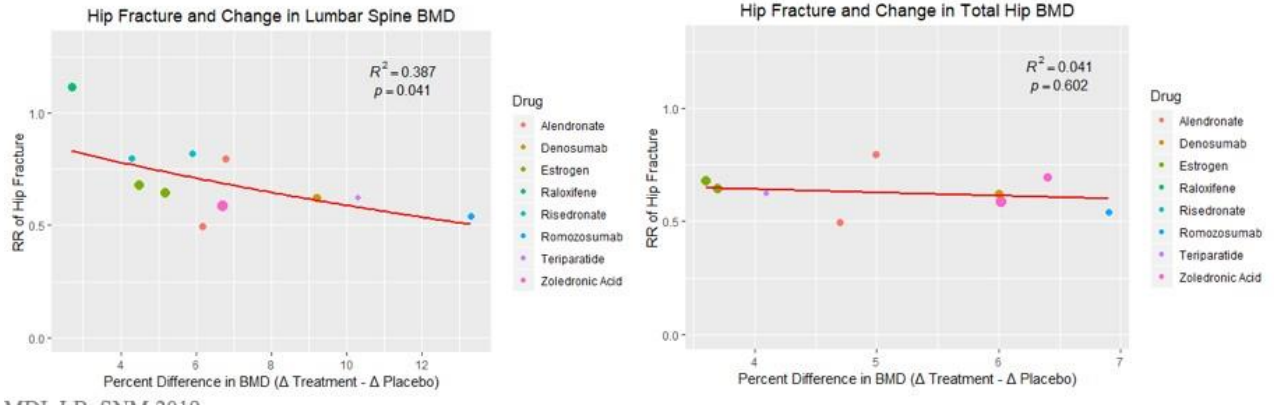
	Δ Total Hip BMD	Δ Lumbar Spine BMD
Vertebral Fracture		
No. Studies Included	11	20
No. of Subjects	57439	68478
No. of Fractures	1631	2609
R^2	0.172	**0.225**
p Value	0.205	**0.035**
Hip Fracture		
No. Studies Included	9	11
No. of Subjects	60194	68227
No. of Fractures	614	663
R^2	0.041	**0.387**
p Value	0.602	**0.041**
Non-Vertebral Fracture		
No. Studies Included	13	20
No. of Subjects	38002	48168
No. of Fractures	2660	3472
R^2	0.210	0.063
p Value	0.117	0.285
Any Fracture		
No. Studies Included	20	29
No. of Subjects	68563	79667
No. of Fractures	6627	8424
R^2	0.007	0.013
p Value	0.734	0.550

Figures:

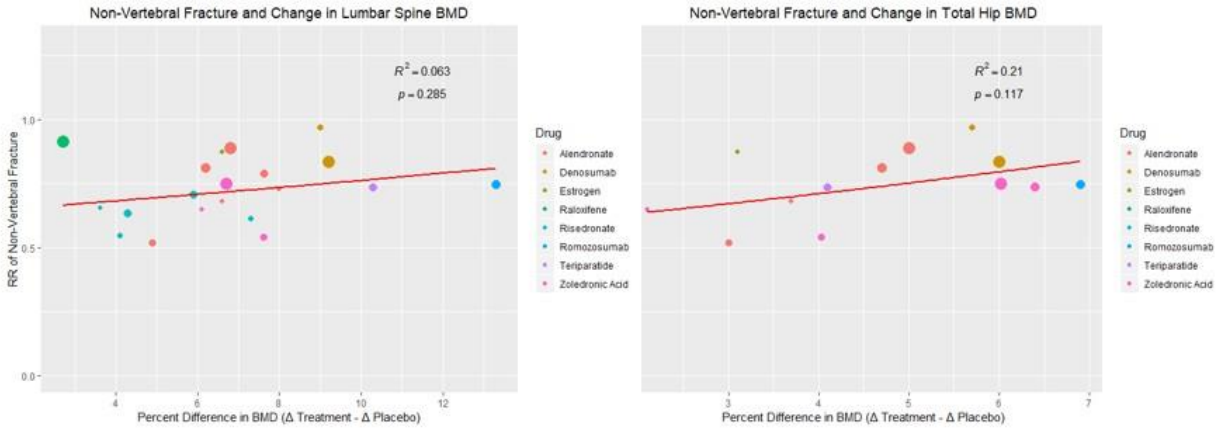
A) Vertebral Fractures



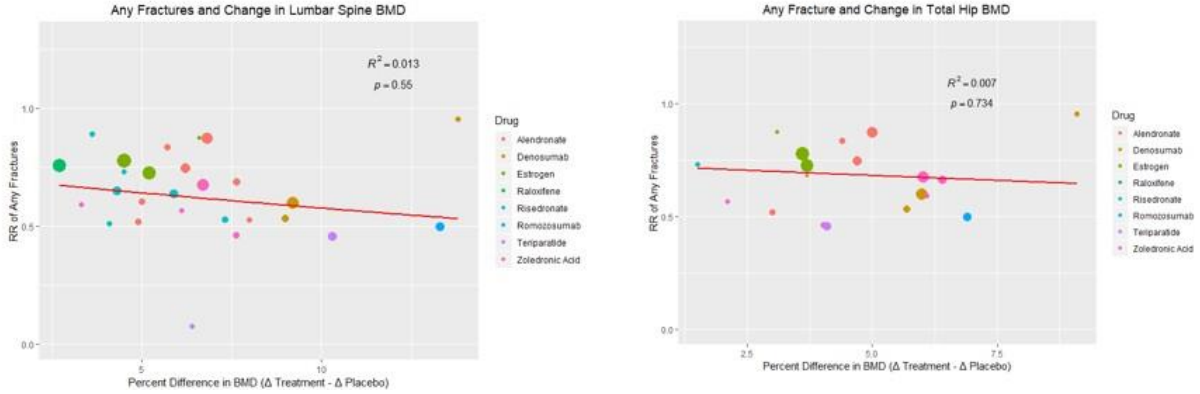
B) Hip Fractures



C) Non-Vertebral Fractures



D) Any Fracture



3. *Does BMD monitoring while on therapy lead to a change in treatment within a treated population?*
We identified only one observational study using data from the Manitoba BMD Registry linked to provincial administrative healthcare data (same study used to answer Q1 above).
In this asssessment the outcome is not fractures but **change in therapy (switch).** It is assumed that the change in treatment is a consequence of BMD increase or decrease. See table below.
Mean BMD interval 3.2 years.

Setting: does a change in BMD results in a change in treatment?
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD change on while on therapy	no BMD change	Relative (95% CI)	Absolute (95% CI)		
SWITCH IN TREATMENT VS SAME TREATMENT (LUMBAR SPINE BMD INCREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINSTRATIVE DATABASE- PHARMA RECORDS)												
1	observational studies	not serious [a]	not serious	serious [b]	not serious	none	107/1190 (9.0%)	371/2487 (14.9%)	**OR 0.61** (0.48 to 0.77)	**53 fewer per 1,000** (from 72 fewer to 30 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
SWITCH IN TREATMENT VS SAME TREATMENT (HIP SPINE BMD INCREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINISTRATIVE DATABASE-PHARMA RECORDS)												
1	observational studies	not serious [a]	not serious	not serious [b]	not serious	none	134/1335 (10.0%)	337/2592 (13.0%)	**OR 0.83** (0.66 to 1.04)	**20 fewer per 1,000** (from 40 fewer to 5 more)	⨁⨁◯◯ LOW	CRITICAL
SWITCHED TREATMENT VS SAME TREATMENT (LUMBAR SPINE BMD DECREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINISTTRATIVE DATABASE-PHARMA)												
1	observational studies	not serious [a]	not serious	serious [b]	not serious	strong association	46/176 (26.1%)	371/2487 (14.9%)	**OR 1.68** (1.12 to 2.52)	**78 more per 1,000** (from 15 more to 157 more)	⨁⨁◯◯ LOW	CRITICAL
SWITCHED TREATMENT VS SAME TREATMENT (HIP SPINE BMD DECREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINISTRATIVE DATABASE-PHARMA)												
1	observational studies	not serious [a]	not serious	serious [b]	not serious	strong association	109/436 (25.0%)	337/2592 (13.0%)	**OR 2.01** (1.49 to 2.73)	**101 more per 1,000** (from 52 more to 160 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. selection bias
b. The reason for treatment change is ascribed to BMD result done prior to treatment change i.e. we do not have the reason for clinician prescription behaviour or patient decision to continue or stop treatment.

We did not identify adverse events from monitoring with BMD; however, there is the possibility of invalid results or erroneous interpretation.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

We did not identify any RCT that evaluated monitoring of BMD on fracture outcomes in patients on antiosteoporosis therapy.
Therefore, the evidence considered for the question on monitoring of BMD in patients while on therapy is presented in answer to 3 sub-questions, relying mostly on **indirect** evidence.

1. *Does monitoring while on therapy lead to a change in fracture outcomes **within a treated** population?*
We found only one observational study using data from the Manitoba BMD Registry linked to provincial administrative healthcare data.
Monitoring interval: mean 3.2 years (SD 0.9);
Outcomes: MOF and Hip fractures over 10 years.
Effect is small to moderate. (see additional considerations)

Question: BMD monitoring compared to no BMD monitoring for reduction in fracture outcomes within a treated population [1]
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD monitoring	no BMD monitoring	Relative (95% CI)	Absolute (95% CI)		
Major osteoporotic fracture (observational study) (follow up: mean 10 years; assessed with: Fracture codes)												
1	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would reduce the demonstrated effect dose response gradient [c]	591/4559 (13.0%)	632/4559 (13.9%)	**HR 0.90** (0.82 to 1.00)	**13 fewer per 1,000** (from 23 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hip fracture (observational study) (follow up: mean 10 years; assessed with: Fracture codes)												
1	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would reduce the demonstrated effect dose response gradient [d]	167/4559 (3.7%)	215/4559 (4.7%)	**HR 0.75** (0.64 to 0.89)	**12 fewer per 1,000** (from 17 fewer to 5 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. Newcastle Ottawa scale> Good quality
b. BMD monitoring is inferred as it is not possible from administrative data to know why MDs decide to repeat or not BMD assessment with DXA.
c. Risk Major osteoporotic fracture in monitored versus non monitored over 10 years: 591/4559 (M) vs 632/4559 (NM)= RR: 0.13/0.14= 0.93 (95% CI 0.84-1.0);; ARR (NM-M) = 0.14-0.13 =0.01 p=0.208; 1.8 MOF/ 1000 person years HR 0.90 95% CI (0.82-1.00) (adjusted analyses)
d. Risk HIP fracture in monitored vs non monitored over 10 years: 167/4559 (M) vs 215/4559 (NM)=RR: 0.04/0.05= 0.78 (95% CI 0.64-0.95)) ARR (NM-M) = 0.05-0.04= 0.01 p=0.012 1.4 HIP / 1000 person years; HR 0.75 95% CI (0.64-0.89) (adjusted analyses)

References

1. Leslie, W.D.,et al.,. Association of Bone Density Monitoring in Routine Clinical Practice With Anti-Osteoporosis Medication Use and Incident Fractures: A Matched Cohort Study.. J Bone Miner Res.; 2019.

2. *Does an observed increase/decrease (vs stability) in the monitoring parameter while **on therapy** predict a difference in **fracture** outcomes within a treated population? (if insufficient data in 4A).*
This is **indirect evidence** as monitoring was not the question of interest in these studies.
We used data from 2 RCT studies evaluating BMD change and fracture outcomes in the **treated** arm of the trials. See table below.
Monitoring interval was 3 years (mean 3.2 y)
The **effect is moderate** depending on the trial and fracture site.

(Of note, other publications were identified, data were presented **as linear regression analyses** with BMD as a continuous variable making it impossible to show the data in GradePro tables.
For example: an increase of BMD of approximately 3 % at 3 years with **alendronate** was associated with a relative reduction of Radiographic VF by 47%. If we use a baseline rate of 15 R VF per 1000 p per year, this would translate in a reduction of 7 RVF per 1000 p-year. *Data not shown*)

Question: BMD change on therapy compared to no BMD change on therapy for predicting fracture outcomes [1234567891011121314151617181920212223242526272829303132 33]
Setting:
Bibliography: [a]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD change on therapy	no BMD change on therapy	Relative (95% CI)	Absolute (95% CI)		
WATTS (2004) VERTEBRAL FRACTURES_ while on treatment (risedronate) lumbar spine BMD Increase (>0%) vs No BMD increase (<0%) (follow up: mean 3 years; assessed with: radiographs)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	9.8/100 (9.8%)	15.5/100 (15.5%)	**RR 0.56** (0.38 to 0.82)	**68 fewer per 1,000** (from 96 fewer to 28 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Jacques 2012 Non vertebral fractures and change in total HIP BMD change while on therapy (follow up: mean 3 years; assessed with: report)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	9.6/100 (9.6%)	7/100 (7.0%)	**OR 0.73** (0.24 to 0.59)	**18 fewer per 1,000** (from 52 fewer to 27 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. only larger RCTs were kept in the analyses (ie placebo groups with at least 50 participants). Most studies identified report positive effects of treatment on BMD
b. indirect evidence because change in BMD while on treatment vs not on treatment (PBO): not our question

We also compiled data from 2 observational studies (using similar population over a different stduy period 9 or 12 years) Data shown here are for the study with timeline of 9 years.
Monitoring interval: mean 4.5 years
Effect was small

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD change on therapy	no BMD change on therapy	Relative (95% CI)	Absolute (95% CI)		
MAJOR OSTEOPOROTIC FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD INCREASE vs no BMD change (follow up: median 9.2 years; assessed with: fracture codes)												
1	observational studies	not serious	not serious	serious [b]	serious [c]	none	234/1995 (11.7%)	446/3333 (13.4%)	**RR 0.86** (0.73 to 1.00) [d]	**19 fewer per 1,000** (from 36 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
MAJOR OSTEOPOROTIC FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD DECREASE VS NO BMD CHANGE (follow up: median 9.2 years)												
1	observational studies	not serious	not serious	not serious	not serious	none	211/1235 (17.1%)	446/3333 (13.4%)	**RR 1.22** (1.03 to 1.43)	**29 more per 1,000** (from 4 more to 58 more)	⨁⨁◯◯ LOW	CRITICAL
HIP FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD INCREASE VS NO BMD CHANGE (follow up: median 9.2 years; assessed with: fracture codes)												
1	observational studies	not serious	not serious	not serious	serious [c]	none	44/1995 (2.2%)	90/3333 (2.7%)	**RR 0.80** (0.56 to 1.15)	**5 fewer per 1,000** (from 12 fewer to 4 more)	⨁◯◯◯ VERY LOW	CRITICAL
HIP FRACTURES (administrative database) and change in total hip BMD WHILE on therapy- BMD decrease vs NO BMD change (follow up: median 9.2 years; assessed with: fracture codes)												
1	observational studies	not serious	not serious	not serious	not serious	none	56/1235 (4.5%)	90/3333 (2.7%)	**RR 1.60** (1.15 to 2.23)	**16 more per 1,000** (from 4 more to 33 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. only larger RCTs were kept in the analyses (ie placebo groups with at least 50 participants). Most studies identified report positive effects of treatment on BMD
b. indirect evidence because change in BMD while on treatment vs not on treatment (PBO): not our question
c. wide CI. crosses null value

Since not many studies evaluated the effectiveness of BMD monitoring strategies, we also have looked at clinical effectiveness evidence that support the change in BMD and fracture outcomes in RCT via meta-regression analysis (change Treatment group – PBO group and Fx risk). We show here Bouxsein (2019) meta-regression analysis. We did perform a meta regression with Rx available in Canada. The results were similar but much less robust than those of Bouxsein. Linear models were created to estimate the relationship between mean percentage difference in BMD –lumbar spine and total hip- (active minus placebo group) and the logarithm of the RR for each fracture site.
Again this is **indirect evidence** comparing BMD change in **treated vs non treated (PBO)** participants in large RCTs and fracture outcomes.

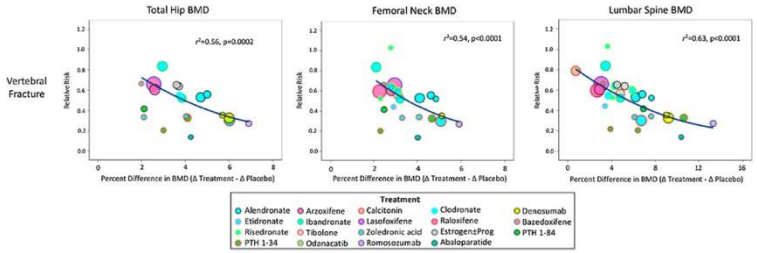


Fig. 1. Association between treatment-related differences in BMD (Active-Placebo, in %) and reduction in vertebral fracture risk. Individual trials are represented by circles with areas that are approximately proportional to the number of fractures in the trial. Drugs of the same class are represented by the symbols of the same color.

Table 5. Estimated Fracture Risk Reduction Associated With BMD Improvement

	Vertebral fracture	Hip fracture	Nonvertebral fracture
Δ Total hip BMD			
2%	28%	16%	10%
4%	51%	29%	16%
6%	66%	40%	21%
Δ Femoral neck BMD			
2%	28%	15%	11%
4%	55%	32%	19%
6%	72%	46%	27%
Δ Lumbar spine BMD			
2%	28%	22%	11%
8%	62%	38%	21%
14%	79%	51%	30%

BMD = bone mineral density.

3. *Does BMD monitoring while on therapy lead to a change in treatment within a treated population?*
We identified only one observational study using data from the Manitoba BMD Registry linked to provincial administrative healthcare data (same study used to answer Q1 above).
In this asssessment the outcome is not fractures but **change in therapy (switch).** It is assumed that the change in treatment is a consequence of BMD increase or decrease. See table below.
Mean BMD interval 3.2 years.

Setting: does a change in BMD results in a change in treatment?
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BMD change on while on therapy	no BMD change	Relative (95% CI)	Absolute (95% CI)		
SWITCH IN TREATMENT VS SAME TREATMENT (LUMBAR SPINE BMD INCREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINSTRATIVE DATABASE- PHARMA RECORDS)												
1	observational studies	not serious [a]	not serious	serious [b]	not serious	none	107/1190 (9.0%)	371/2487 (14.9%)	**OR 0.61** (0.48 to 0.77)	**53 fewer per 1,000** (from 72 fewer to 30 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
SWITCH IN TREATMENT VS SAME TREATMENT (HIP SPINE BMD INCREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINISTRATIVE DATABASE-PHARMA RECORDS)												
1	observational studies	not serious [a]	not serious	not serious [b]	not serious	none	134/1335 (10.0%)	337/2592 (13.0%)	**OR 0.83** (0.66 to 1.04)	**20 fewer per 1,000** (from 40 fewer to 5 more)	⨁⨁◯◯ LOW	CRITICAL
SWITCHED TREATMENT VS SAME TREATMENT (LUMBAR SPINE BMD DECREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINISTTRATIVE DATABASE-PHARMA)												
1	observational studies	not serious [a]	not serious	serious [b]	not serious	strong association	46/176 (26.1%)	371/2487 (14.9%)	**OR 1.68** (1.12 to 2.52)	**78 more per 1,000** (from 15 more to 157 more)	⨁⨁◯◯ LOW	CRITICAL
SWITCHED TREATMENT VS SAME TREATMENT (HIP SPINE BMD DECREASE VS NO CHANGE); INTERVAL BETWEEN DXA SCANS 3.2 Y (follow up: mean 10 years; assessed with: ADMINISTRATIVE DATABASE-PHARMA)												
1	observational studies	not serious [a]	not serious	serious [b]	not serious	strong association	109/436 (25.0%)	337/2592 (13.0%)	**OR 2.01** (1.49 to 2.73)	**101 more per 1,000** (from 52 more to 160 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. selection bias
b. The reason for treatment change is ascribed to BMD result done prior to treatment change i.e. we do not have the reason for clinician prescription behaviour or patient decision to continue or stop treatment.

We did not identify adverse events from monitoring with BMD; however there is the possibility of invalid results or erroneous interpretation.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	There are no RCT data with **direct evidence** that support the effect of monitoring BMD on fracture reduction while on therapy. The certainty of the evidence that is most directly in answer to our question is very low (leslie et al 2019); observational study However, indirect evidence is of higher certainty

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Fracture Outcomes are highly valued by patients. BMD Monitoring is also highly valued by patients It is also promoted by Patient societies (OC, IOF, NOF) There have been considerable efforts by many organizations to ensure that patients obtain BMD testing and are aware of their T-score. This is not only for initial screening but has also been perceived by patients as being important in monitoring of treatment. In the most recent COPN survey, to the question: **"Provide up to three specific questions you would like to see addressed in the next Canadian Osteoporosis Clinical Practice Guidelines''** there were 88 citations on BMD tests/ response to treatment (out of 193 citations in the theme of Screening-Monitoring).	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	In patients whose BMD is decreasing, an increase in the risk of fractures (HIP) was documented over the 10 years follow up (observational study. Leslie et al 2019). BMD changes are associated with change in treatment. In PBO controlled studies, treatement associated with increases in BMD associate positively with fracture reduction.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There is a cost associated with repeating BMD and with re-evaluation. However, it is CURRENT practice to monitor BMD when patients are on treatment, sometimes as frequently as yearly. Hence if guidance is provided as to the ''optimal'' interval of monitoring, it may in fact reduce costs if at longer interval than currently performed.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	BMD measurment by DXA technology is well established. The cost for the test (including technician time and expertise, and radiologist interpretation) is similar in each province. It is not a very expensive radiological test. There are limitations in terms of access in rural / remote communities.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Access is a problem in rural / remote communities.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	This test is readily accepted and sought after by patients. Clinicians also believe the test is important for monitoring the effect of the treatment and possibly as a form of encouragement for better adherence to the management plan.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	Yes. DXA machines available across the country, except in rural / remote communities	

○ Varies ○ Don't know	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Conditional recommendation (VERY low level of evidence)

We suggest BMD measurement 3 years after *initiating* pharmacotherapy.

Justification

Based on a review of the evidence, we conclude that there is **low** level evidence to support this recommendation as the large majority of the evidence is indirect in nature.
The effect was found to be small to moderate, depending on the fracture outcome studied.
Furthermore, the observational studies that contribute to the evidence arise from one province (Manitoba). Nevertheless, the evidence does support the association between BMD improvement and fracture reduction.
There is insufficient evidence to make a recommendation on the frequency of ongoing BMD monitoring following the initial follow-up BMD.
BMD monitoring is **highly valued** by patients and very established in clinical practice. It has little undesirable effects (low radiation, non-invasive, short duration for image acquisition).
This recommendation aims to provide a specific interval for repeat scanning- this may lead to a reduction in BMD tests overtime (currently serial BMDs are performed too frequently) . Costs associated with BMD monitoring might then decrease.
This recommendation should be acceptable to patients and clinicians, **though the specific interval of 3 years is a change from previous practice**, and feasible to apply- if some exceptions are allowed in various jurisdictions as per clinicians' judgement.

Subgroup considerations

There are no data in men regarding our primary question.

Implementation considerations

Monitoring and evaluation

Research priorities

Males
More research is required in the area of monitoring on clinical outcomes, including patient satisfaction.
Effect of long-term monitoring (multiple repeat BMD tests) on treatment and fracture outcomes.

QUESTION 4B: BONE TURNOVER MARKER

SHOULD WOMEN (MEN) AGED 50 YEARS OR OLDER RECEIVING TREATMENT TO PREVENT FRACTURES BE MONITORED WITH REPEAT DXA, FRACTURE RISK SCORE WITH DXA (E.G., FRAX, CAROC), BONE TURNOVER MARKERS (BTM) VERSUS CLINICALLY (NO SPECIFIC TESTING)?

Should BTM monitoring vs. no BTM monitoring be used for reduction in fracture outcomes in men and women while on anti-osteoporosis therapy?	
POPULATION:	reduction in fracture outcomes in men and women while on anti-osteoporosis therapy
INTERVENTION:	BTM monitoring
COMPARISON:	no BTM monitoring
MAIN OUTCOMES:	
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Osteoporosis** poses an immense burden to the society in terms of morbidity, mortality and financial **cost**. To reduce this burden, it is essential to accurately assess the individual patient's fracture risk and, where indicated, to initiate appropriate treatment that reduces fracture probability. Current **monitoring** approaches include utilization of bone turnover markers (formation and resorption). The use of BTMs varies depending on geographical area and whether treating physician is a primary care MD vs a specialist. **Monitoring while on therapy** is a very important issue to patients, clinicians and policy makers.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**WE SOUGHT TO ANSWER 2 QUESTIONS:** **1. Should BTM change while on therapy vs. no BTM change while on therapy be used for predicting fracture outcomes?** **DIRECT EVIDENCE** **No** clinical trials evaluated the effectiveness of BTMs monitoring strategies (vs no monitoring) on **fracture outcomes in patients on treatment.** Most of the evidence available was in the form of correlations between changes in bone turnover marker levels and BMD **(ie association between change in BTMs and change in BMD) .** The usefulness of correlation data to inform the accuracy of bone turnover marker tests for identifying patients at risk of fracture **was limited.**

In addition there are limitation inherent to BTMs in view of:

- The many different types of BTMs used in the various RCTs (urinary, serum, resorption vs formation, old or new)
- The timing of sampling of the BTMs (3 to 12 months) following initiation of Rx
- The timing of fracture assessment relative to measure of BTMs

INDIRECT EVIDENCE

Since not many studies evaluated the effectiveness of BTMS monitoring strategies, we also have looked at clinical effectiveness evidence that support the change in BTM (TREATED VS PBO) and fracture outcomes in RCT via meta-regression analysis.

Bauer[36], D.C., et al., *Treatment-Related Changes in Bone Turnover and Fracture Risk Reduction in Clinical Trials of **Anti-Resorptive** Drugs: A Meta-Regression. J Bone Miner Res, 2018. 33(4): p. 634-642*.

It follows a similar method as the one of Mary Bouxsein, used for BMD analysis.

This meta-regression analysis provides **individual patient level** data on **short term BTM median change %** and **fracture outcomes** using data from osteoporosis pivotal trials up to 2012 on the following medications:

Alendronate, Risedronate, Zoledronic acid and Raloxifene **+** Ibandronate and Arzoxifene and Lasofoxifene

*Denosumab was not retained in this analysis because too few participants had serial BTMs measured (n=80 per group)

(We also extracted the data from the studies we had identified (including those from Bauer but excluding from our table those studies evaluating Rx not available in Canada). Our overall results, though not meta-analyzed, were consistent with the results of Bauer's and are not shown here**)**

Table 4. Meta-Regression Summary for Short-Term Changes in BTMs and Fracture Risk Reduction

	Vertebral			Nonvertebral			Hip		
BMTs	Studies *n* (fractures)	r^2 (95% CI)	*p*	Studies *n* (fractures)	r^2 (95% CI)	*p*	Studies *n* (fractures)	r^2 (95% CI)	*p*
Bone ALP	11 (3284)	0.82 (0.50–0.88)	<0.001	12 (4615)	0.33 (0.00–0.57)	0.053	12 (653)	0.17 (0.00–0.47)	0.24
PINP	7 (2780)	0.75 (0.17–0.85)	0.011	7 (4454)	0.53 (0.00–0.73)	0.065	7 (612)	0.43 (0.00–0.67)	0.11
NTX/Cr	8 (1639)	0.38 (0.00–0.64)	0.10	9 (2500)	0.25 (0.00–0.54)	0.17	9 (366)	0.03 (0.00–0.34)	0.73
sCTX	5 (1780)	0.62 (0.00–0.78)	0.11	5 (2865)	0.47 (0.00–0.71)	0.20	5 (350)	0.20 (0.00–0.56)	0.45
IRMA and ELISA BMTs[a]									
Bone ALP	7 (1701)	0.52 (0.00–0.72)	0.066	8 (2704)	0.33 (0.00–0.61)	0.13	8 (376)	0.10 (0.00–0.47)	0.53
NTX/Cr	6 (1293)	0.41 (0.00–0.67)	0.17	7 (2244)	0.31 (0.00–0.60)	0.20	7 (334)	0.03 (0.00–0.38)	0.78

[a]Bone ALP Ostase Tandem IRMA assay and NTX/Cr with Osteomark ELISA assay.

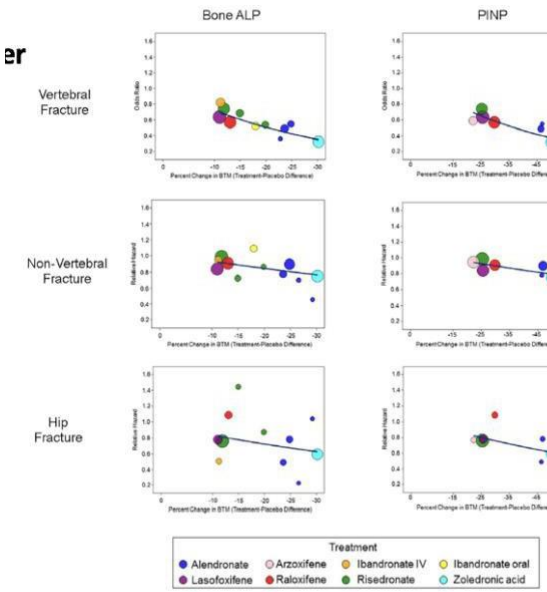


Fig. 1. The relationship between the odds ratio (for vertebral fracture) or the relative hazard (for nonvertebral and hip fracture) and the difference between treatment and placebo group in percentage change in BTM for the two bone formation markers. Larger circles indicate studies with more fractures, and the line represents log relative risk plotted against percent change.

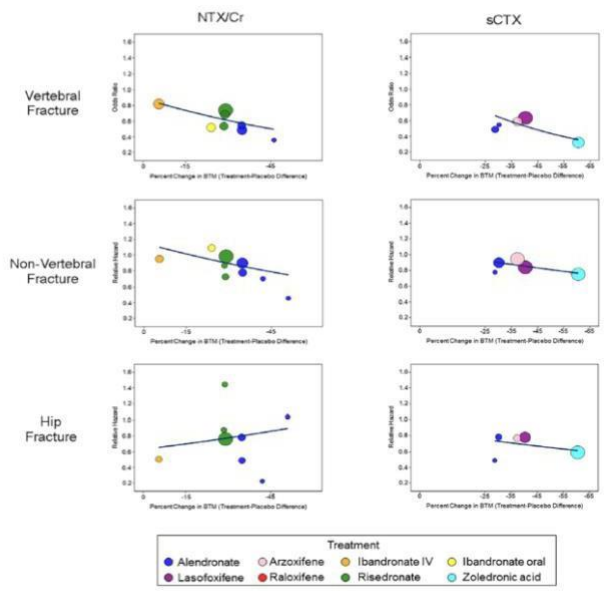


Fig. 2. The relationship between the odds ratio (for vertebral fracture) or the relative hazard (for nonvertebral and hip fracture) and the difference between treatment and placebo group in percentage change in BTM for the two bone resorption markers. Larger circles indicate studies with more fractures, and the line represents log relative risk plotted against percent change.

We used the above data from Bauer and applied to baseline Vertebral fractures rates and estimated the V Fx risk reduction associated with short term change in Bone Alk Phosph and P1NP (the only 2 markers that demonstrated significant associatin with fracture risk in the metaregression analysis).

Estimated Vertebral Fracture risk reduction and difference between treatment and placebo in Bone Alk Phosp and P1NP using baseline risk vertebral fractures (5/1000-py)

Median difference (Tx-PBO) in % change: Bone Alk Phosph	**VFx RR**	**VFx Reduction** /1000 p-years
		Baseline 5
12%	33%	1.7
30%	65%	3.25
Median difference (Tx-PBO) in % change: P1NP		
22%	30%	1.5
50%	62%	3.1

Based on the criteria used by Bauer and Bouxsein, we identifIED studies with ANABOLIC agents (Romozosumab and Teriparatide) that met the following criteria:

1. placebo-controlled randomized trials,
2. BTM (osteocalcin, bone alkaline phosphatase, P1NP, NTX and CTX) at baseline and follow-up minimum 3 months (max 12 months)
3. data for fracture endpoints available (same as for Bauer analysis)
4. We did not proceed with a meta-regression but report the results in a narrative fashion.

For **teriparatide**, an increase in osteocalcin (+15%) and P1NP (+7 -10%) was associated with a decrease in fractures (Vert Fx RR 0.20 (95% CI 0.09-0.42); NonVert FX: RR 0.87 (95% CI 0.42- 1.79).
For **romosozumab**, an early increase in P1NP and decrease CTx was associated with a reduction in fractures. Only one study.

Finally, we also identified 3 systematic reviews. **None performed meta-analyses.**
We report their concluding statements:
1. Health Technology Assessment (Vol 18, Issue 11; Feb **2014**) Systematic review of the use of BTM for monitoring response to osteoporosis treatment
"The lack of evidence of clinical effectiveness and the heterogeneity and poor quality of the available evidence on the accuracy, reliability and reproducibility of bone turnover markers for monitoring response to osteoporosis treatment precluded the possibility of making any recommendations on the choice of bone turnover marker being used in routine clinical practice for its superiority to monitor osteoporosis treatment response. In addition, the evidence to support the use of bone turnover marker feedback results to improve patient adherence to osteoporosis treatment was not convincing."

2. Funck-Brentano et al. (Seminars in Arthritis and Rheumatism **2011**) Clinical Utility of serum BTMs in postmenopausal osteoporosis therapy monitoring: a systematic review
"BTM reflect the skeletal effects of anti-osteoporotic treatments. Pretreatment values are not recommended for selecting therapy. Short-term changes are significantly correlated with BMD variation, but there is no published evidence that they predict benefit on fracture risk at the individual level."

3. Vasikaran et al (Osteoporos Int **2011**) Markers of bone turnover for the prediction of fracture risk and monitoring of osteopeorosis: a need for international reference standards
"*However, their (BTMs) clinical value for monitoring is limited by inadequate appreciation of the sources of variability, by limited data for comparison of treatments using the same BTM and by inadequate quality control."*

2. Should change in BTM vs. no change in BTM be used for changing medical therapy?
We were unable to identify primary studies to answer this question

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

WE SOUGHT TO ANSWER 2 QUESTIONS:
1. Should BTM change while on therapy vs. no BTM change while on therapy be used for predicting fracture outcomes?

DIRECT EVIDENCE
No clinical trials evaluated the effectiveness of BTMs monitoring strategies (vs no monitoring) on **fracture outcomes in patients on treatment.**
Most of the evidence available was in the form of correlations between changes in bone turnover marker levels and BMD **(ie association between change in BTMs and change in BMD) .**
The usefulness of correlation data to inform the accuracy of bone turnover marker tests for identifying patients at risk of fracture **was limited.**

In addition there are limitation inherent to BTMs in view of:

- The many different types of BTMs used in the various RCTs (urinary, serum, resorption vs formation, old or new)
- The timing of sampling of the BTMs (3 to 12 months) following initiation of Rx
- The timing of fracture assessment relative to measure of BTMs

INDIRECT EVIDENCE
Since not many studies evaluated the effectiveness of BTMS monitoring strategies, we also have looked at clinical effectiveness evidence that support the change in BTM (TREATED VS PBO) and fracture outcomes in RCT via meta-regression analysis.

Bauer[36], D.C., et al., *Treatment-Related Changes in Bone Turnover and Fracture Risk Reduction in Clinical Trials of **Anti-Resorptive** Drugs: A Meta-Regression. J Bone Miner Res, 2018. 33(4): p. 634-642*.
It follows a similar method as the one of Mary Bouxsein, used for BMD analysis.
This meta-regression analysis provides **individual patient level** data on **short term BTM median change %** and **fracture outcomes** using data from osteoporosis pivotal trials up to 2012 on the following medications:
Alendronate, Risedronate, Zoledronic acid and Raloxifene **+** Ibandronate and Arzoxifene and Lasofoxifene
*Denosumab was not retained in this analysis because too few participants had serial BTMs measured (n=80 per group)

(We also extracted the data from the studies we had identified (including those from Bauer but excluding from our table those studies evaluating Rx not available in Canada). Our overall results, though not meta-analyzed, were consistent with the results of Bauer's and are not shown here**)**

Table 4. Meta-Regression Summary for Short-Term Changes in BTMs and Fracture Risk Reduction

	Vertebral			Nonvertebral			Hip		
BMTs	Studies *n* (fractures)	r^2 (95% CI)	*p*	Studies *n* (fractures)	r^2 (95% CI)	*p*	Studies *n* (fractures)	r^2 (95% CI)	*p*
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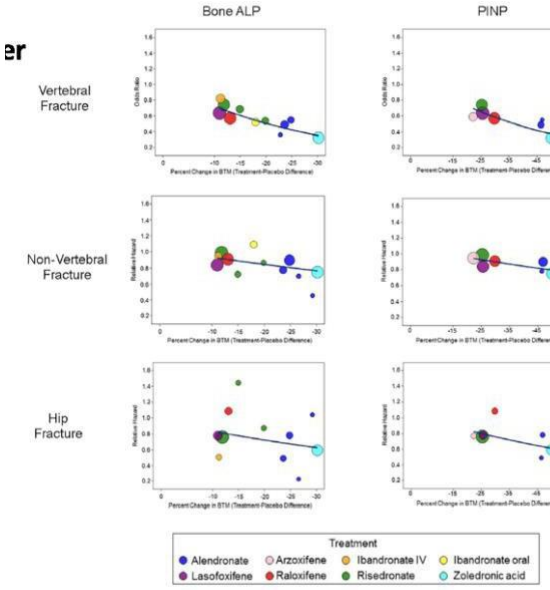

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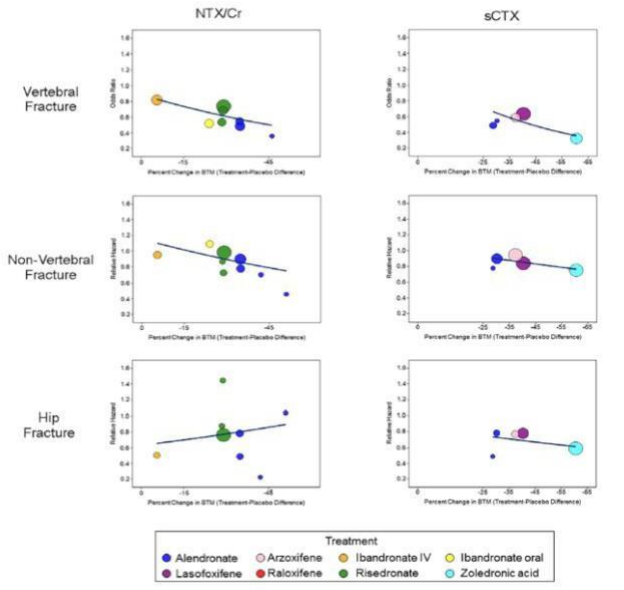

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	2. Should change in BTM vs. no change in BTM be used for changing medical therapy? We were unable to identify primary studies to answer this question

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**No direct evidence.** **Indirect evidence:** good level evidence that a decrease in bone formation BTM is associated with a reduction in vertebral fractures with use of antiresorptive agents (metaregression with individual level data of multiple large PBO controlled RCTs).	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Fracture outcomes are highly valued by patients. Monitoring in general is also highly valued by patients- but patients are not widely aware of monitoring by BTM. BTM monitoring (mostly for adherence monitoring) is recommended by ECTS, IOF, NOF In the most recent COPN survey, to the question: **"Provide up to three specific questions you would like to see addressed in the next Canadian Osteoporosis Clinical Practice Guidelines"** there were 88 citations on BMD tests/ response to treatment (out of 193 citations in the theme of Screening-Monitoring).	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No direct evidence to support our question. Indirect evidence may favor the intervention of monitoring- but multiple issues limit the vaidity of the data presented.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Increased costs would be associated with the routine measurement of BTMs for monitoring of patients at this time, in view, for example of the issue of reproducibility of BTM levels measured by commercial laboratories, the thresholds to effect a change in therapy, etc.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ● High ○ No included studies	One may consider an alternative algorithm be put in place whereby we would monitor patients with BTMs instead of using BMD. Costs might then be mitigated. However, no data have looked at the effectiveness of such an approach- so this would be speculative at this point.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	we did not study cost-effectiveness	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Currently many centres do not have access to BTM measurements and/or they are not reimbursed by provincial health insurance programs. So equity would be reduced on the basis of differential availabity and reimbursement between provinces or private insurance programs.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	This would likely be acceptable to patients and to clinicians if BTMs were wideley available and results reliable, and if they became familiar with their interpretation. BTM are used currently in some jursidcitions to monitor therapy; not to predict fracture reduction	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Costs, type of assay, expertise in interpretation prohibit easy implementation At this time, it would be difficult to implement in routine primary care.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	**No**	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

Conditional recommendation (very low-certainty evidence) against using BTM for monitoring females and males using bone turnover markers after initiating pharmacotherapy to prevent fractures

Justification

There is no direct evidence available.
The indirect evidence supports an association between short-term change in bone formation markers and vertebral fractures.
There are many limitations with BTM measurements currently, including lack of standard thresholds, commercial assays variability, clinical algorithms -intervals at which they should be measured, how frequently, etc-.
Furthermore, significant costs would be associated with implementation of BTMs in routine clinical practice, unless unless they were to replace BMD monitoring early (3 months) following initiation of therapy
BTMs are currently used frequently by bone metabolism specialists for specific conditions. Maybe there could be a statement to this effect (and the underpinning) in the text of the guidelines.

Subgroup considerations

Need data in men, in women, in special groups, etc.

Implementation considerations

-

Monitoring and evaluation

-

Research priorities

The predictive accuracy of bone turnover markers for future fracture outcomes in patients receiving osteoporosis treatment must be investigated prospectively (large cohorts or RCT) using standard measurement intervals and selected analytes.

QUESTION 4C: FRAX

SHOULD WOMEN (MEN) AGED 50 YEARS OR OLDER RECEIVING TREATMENT TO PREVENT FRACTURES BE MONITORED WITH REPEAT DXA, FRACTURE RISK SCORE WITH DXA (E.G., FRAX, CAROC), BONE TURNOVER MARKERS (BTM) VERSUS CLINICALLY (NO SPECIFIC TESTING)?

Should FRAX change vs. no FRAX change be used for predicting fracture outcomes?	
POPULATION:	predicting fracture outcomes
INTERVENTION:	FRAX change
COMPARISON:	no FRAX change
MAIN OUTCOMES:	FRAX (WITH BMD) change (mean interval between DXA scans: 3.8 years) and Major Osteoporosis Fractures in women; N= 11049; FRAX (WITH BMD) change (mean interval between DXA scans: 3.8 years) and Hip Fractures in women; N=11049;
SETTING:	cohort study
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Osteoporosis** poses an immense burden to the society in terms of morbidity, mortality and financial **cost**. To reduce this burden, it is essential to accurately assess the individual patient's fracture risk and, where indicated, to initiate appropriate treatment that reduces fracture probability. Current **monitoring** approaches, while on therapy, can include utilization of fracture risk assessment tool such as FRAX or CAROC (in Canada). Monitoring while on therapy is a very important issue to patients, clinicians and policy makers to evaluate the impact of treatment on fracture risk FRAX is not frequently used to monitor patients, but has been raised as a potential tool for monitoring.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found only one observational study: Leslie, W.D., et al., *Can change in FRAX score be used to "treat to target"? A population-based cohort study*. J Bone Miner Res, 2014. **29**(5): p. 1074-80. FRAX scores for the entire study cohort increased over the study period, despite stable Femoral Neck BMD, and also increased in the subgroup highly adherent to treatment (MPR≥0.80) despite an increase in Femoral Neck BMD.	

Overall FRAX MOF increased by 1.1% (IQR 0.4-2.3) and FRAX HIP fractures increased by 0.3% (IQR 0.0-0.8).
Thus, serial FRAX measurements are unlikely to be useful in monitoring patients while on therapy.

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without FRAX change	With FRAX change	Difference		
FRAX (WITH BMD) change (mean interval between DXA scans: 3.8 years) and Major Osteoporosis Fractures in women; N= 11049 (MOF) assessed with: fracture codes in medical health records follow-up: mean 4 years № of participants: 11049 (1 observational study)	FRAX SCORES FOR THE ENTIRE STUDY COHORT INCREASED OVER THE STUDY PERIOD, DESPITE STABLE FNECK BMD.Incident MOF; N= 620HR for incident MOF in those with largest FRAX change (vs smallest)HR 1.05 (95% CI 0.81-1.35) p;0.763				⨁◯◯◯ Very low[a]	
FRAX (WITH BMD) change (mean interval between DXA scans: 3.8 years) and Hip Fractures in women; N=11049 (Hip) assessed with: fracture codes in medical health records follow-up: mean 4 years № of participants: 11049 (1 observational study)	FRAX SCORES FOR THE ENTIRE STUDY COHORT INCREASED OVER THE STUDY PERIOD, DESPITE STABLE FNECK BMD.Incident Hip fracture: N=152HR for incident hip fracture inthose with largest FRAX change (vs smallest change):HR 1.14 (95%CI 0.69-1.91) p: 0.205				⨁◯◯◯ Very low[a]	

a. wide confidence intervals , particularly in highly adherent subgroup

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	We found only one observational study: Leslie, W.D., et al., *Can change in FRAX score be used to "treat to target"? A population-based cohort study.* J Bone Miner Res, 2014. **29**(5): p. 1074-80. FRAX scores for the entire study cohort increased over the study period, despite stable Femoral Neck BMD, and also increased in the subgroup highly adherent to treatment (MPR≥0.80) despite an increase in Femoral Neck BMD. Overall FRAX MOF increased by 1.1% (IQR 0.4-2.3) and FRAX HIP fractures increased by 0.3% (IQR 0.0-0.8). This is mostly due to increasing age and accumulation of risk factors **Thus, serial FRAX measurements are unlikely to be useful in monitoring patients while on therapy.**	

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Certainty of evidence

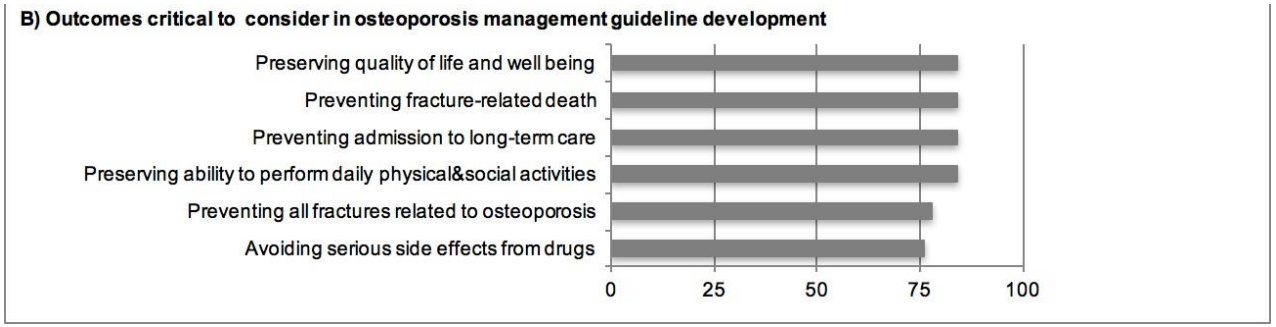
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There were no RCT data available in response to our question We identified one observational study, in women only. Very low certainty. No data on CAROC but expected to be much less treatment-responsive than FRAX since it is based upon risk categories.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	 Percentage of respondents (COPN survey) who indicatedspecific outcomes critical to consider in OP clinical guideliens development **Fracture Outcomes are highly valued by patients.** **Monitoring is also highly valued by patients** It is also promoted by multiple societies (OC, IOF, NOF) In the most recent COPN survey, to the question: **"Provide up to three specific questions you would like to see addressed in the next Canadian Osteoporosis Clinical Practice Guidelines"** there were 88 citations on BMD tests/ **response to treatment** (out of 193 citations in the theme of Screening-Monitoring). BTMs monitoring could be viewed as monitoring response to treatment

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	FAVOURS **NO MONITORING** of FRAX FOR PREDICTING FRACTURE OUTCOMES in treated patients.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Cost of repeat BMD testing, but in addition requires accurate information on clinical risk factors.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	BMD-associated costs would have to be considered.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included		

studies	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	BMD access can be difficult in rural / remote communities. FRAX is not currently widely used by radiologists. However, FRAX can be used without BMD but is not treatment-responsive since BMD is the only treatment-responsive input to FRAX.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No evidence. However, FRAX monitoring would be acceptable to stakeholders, if it were shown to have a positive effect.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility would be similar initial Fracture risk assessment screening (with or without BMD). Knowledge of clinical factors part of the FRAX must be collected.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

Conditional Recommendation (very low certainty evidence)
We recommend against using FRAX calculations for the puprose of monitoring females and males 50 years and older on pharmacotherapy to prevent fractures.

Justification

Based on a review of the evidence, we conclude that there is **very low** level evidence to support a recommendation on use of FRAX in the monitoring of patients after starting pharmacotherapy as we have only identified **one observational study in women.**
Furthermore there was no association between FRAX change while on therapy and fracture outcomes.
Monitoring is **highly valued** by patients and very established in clinical practice, usually with **BMD- not with FRAX probabilities.**

There is **no benefit** (though probably not much harm) in monitoring FRAX in patients on treatment.

Subgroup considerations

NO data in men

Implementation considerations

-

Monitoring and evaluation

-

Research priorities

Clinical trial (individual level) data (treatment arm) might provide useful information

QUESTION 5A BONE MINERAL DENSITY CHANGE WHILE ON A BISPHOSPHONATE INTERRUPTION (DRUG HOLIDAY)

SHOULD WOMEN (MEN) AGE 50 YEARS OR OLDER CURRENTLY ON A BISPHOSPHONATE INTERRUPTION OR HIATUS (BH) BEING MONITORED WITH REPEAT DXA, FRACTURE RISK SCORE WITH DXA (E.G., FRAX, CAROC), BONE TURNOVER MARKERS (BTM) VERSUS CLINICALLY (NO SPECIFIC TESTING)?

Should BMD change while on bisphosphonate interruption vs. BMD stability be used for predicting fracture outcome?	
POPULATION:	predicting fracture outcome
INTERVENTION:	BMD change while on bisphosphonate interruption
COMPARISON:	BMD stability
MAIN OUTCOMES:	FLEX_Risk of any non spine or clinical vertebral fracture after discontinuing alendronate- BMD decrease at the Femoral Neck (Tertile with highest decrease vs 2 other tertiles); FLEX_Risk of any non spine or clinical vertebral fracture after discontinuing alendronate- BMD decrease at the Total HIP (More or equal to 3% decrease);
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes **Osteoporosis** poses an immense burden to the society in terms of morbidity, mortality and financial **cost**. To reduce this burden, it is essential to accurately assess the individual patient's fracture risk and, where indicated, to initiate appropriate treatment that reduces fracture probability. Current **monitoring** approaches include utilization of FRAX, a web-based country-specific fracture risk assessment tool, bone mineral density measurement by Dual Energy X-ray Absorptiometry (DXA) and bone turnover markers (formation and resorption). Bisphosphonate treatment tinterruption (drug holiday) after 3 to 5 years of bisphophonates is recommended by many CPG. Monitoring while on **drug holiday** is a very important issue to patients, clinicians and policy makers. Already most patients receive BMD to monitor response while not on therapy often with intervals as short as 12 months. FRAX and BTMs as monitoring tools to reduce fracture outcomes are less frequently used due to insufficient evidence and or costs.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

Does an observed increase/decrease (vs stability) in BMD following the interruption of bisphosphonate therapy (drug holiday) predict a difference in fracture outcomes?

•**Data come from extension studies of pivotal trials:**
FIT-FLEX: 10 y ALN vs 5 y ALN+ 5 PBO (1099 women)
Zoledronic A: 6y Zol PBO vs 3 + 3y PBO (1233 women)
Zoledronic A: 9 y Zol vs 6 y Zol + 3 PBO (190 women)
Risedronate: no control (PBO) group

• administrative database studies are not helpful in answering this question as they do not provide information on BMD change while off bisphosphonates

•Most studies examined **fracture risk** while during a drug holiday comparing to on treatment, rather than **BMD change** to predict fracture risk
•Many studies examined BMD and other clinical risk factors at time of entry in the extension phase study as a predictor of fractures as opposed to change in parameter while off Rx

DIRECT EVIDENCE
•Only **one** study documents change in BMD over time on fracture risk **while off treatment**: Bauer 2014 (FLEX):

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BMD stability	Risk difference with BMD change while on bisphosphonate interruption
FLEX_Risk of any non spine or clinical vertebral fracture after discontinuing alendronate- BMD decrease at the Femoral Neck (Tertile with highest decrease vs 2 other tertiles) assessed with: radiographs or clinically follow-up: mean 2 years	0 (1 observational study)	⨁◯◯◯ Very low[a]	**HR 1.51** (0.93 to 2.44)	Study population	
				0 per 1,000	-- **per 1,000** (-- to --)
FLEX_Risk of any non spine or clinical vertebral fracture after discontinuing alendronate- BMD decrease at the Total HIP (More or equal to 3% decrease) assessed with: radiographs or clinically follow-up: mean 2 years	0 (1 observational study)	⨁⨁◯◯ Low[a,b]	**HR 1.68** (1.05 to 2.72)	Study population	
				0 per 1,000	-- **per 1,000** (-- to --)

a. wide CI
b. selection bias

A) Intra-patient BMD CHANGE AND FRACTURE RISK (off treatment): FLEX (437 women on PBO following ALN)

No	Author (year) Sample size (N) Duration	Drug	Sex		Tertile with greatest decrease vs other 2	Risk of Fractures HR (95% CI) 2 year change	Level of bias
			M	W		Any non spine or clinical vertebral	
1	**Bauer (2014)** N= 1099 **437 placebo** and 662 ALN Study duration: 8-10 years; DH after 4-5 yrs of Rx	ALN		W	F Neck Total Hip ≥3% decrease: F Neck Total Hip	1.51 (0.93- 2.44) 1.56 (0.97-2.52) 1.45 (0.90-2.35) **1.68 (1.05-2.72)**	HIGH

Results were similar at 3 years or at lumbar spine BMD (done only at 3 years)

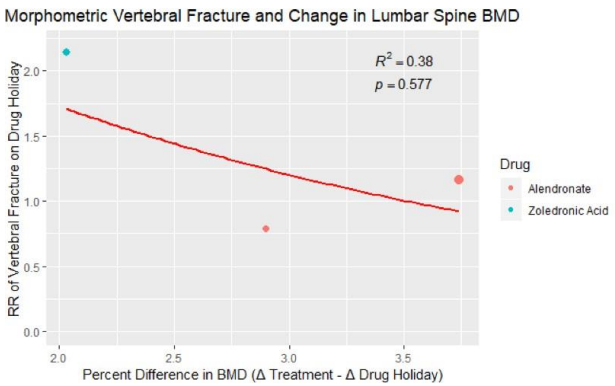
INDIRECT EVIDENCE

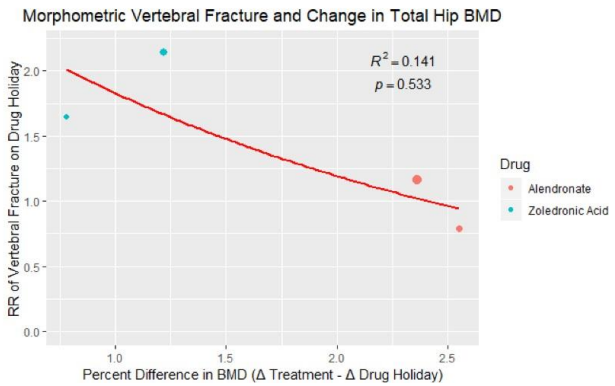
Using similar methodology as Bouxsein and Bauer *Q4 , we performed a meta-regression analysis (BMD change in participants ON vs participants OFF (PBO) bisphosphonates and fracture risk). There was no significant association between change in BMD and morphometric vertebral fractures (data shown), clinical vertebral fractures or non vertebral fractures (data not shown).

A) BMD CHANGE (OFF TREATMENT-DRUG CONTINUATION VS. DISCONTINUATION-PBO) AND FRACTURE RISK:

No	Author (year) Sample size (N) Duration	Drug	Sex		Difference in BMD, active-placebo (%)			Fracture reduction RR (n fractures)					Level of bias
			M	W	TH	FN	LS	Morphometric Vertebral fracture	Clinical Vertebral fracture	Hip fracture	Nonvertebral fracture	All fracture	
References from Fink 2019, Dennison 2019 and references from our search													
1	**Tonino(2000)** N= 350 Study duration: 7 years; DH after 5 yrs of Rx	ALN		W	-	0.87%	1.33%		RR 0.92 CI (0.40,2.10)	-	RR 0.87 CI (0.40,1.91)	-	High
2	**Bone (2004)** N=994 10 years, DH after 5 yrs	ALN		W	2.55%	3.15%	2.9%	RR 1.40 CI (0.52,3.74)		-	RR 0.81 CI (0.38,1.71)	-	High
3	**Black (2006)** N=1099 6 years	ALN		W	2.36%	1.94%	3.74%	RR 0.86 CI (0.60,1.22)	**RR 0.45** **CI (0.24,0.85)**	RR 1.02 CI (0.51,2.10)	RR 1.00 CI (0.76,1.32)	RR 0.93 CI (0.71,1.21)	High
4	**Black (2012)** N=1233 6 years, DH after 3 yrs	Zoledronic acid		W	1.22%	1.04%	2.03%	**RR 0.47** **CI (0.25,0.87)**		RR 1.17 CI (0.39,3.45)	RR 0.96 CI (0.65,1.42)		High
5	**Black (2015)** N=190 9 years, DH after 6 yrs	Zoledronic acid		W	0.78%	0.06%	-	RR 0.61 CI (0.15,2.61)		-	-	RR 1.11 CI (0.47,2.61)	High

A) Morphometric Vertebral Fractures





Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**<u>Does an observed increase/decrease (vs stability) in BMD following the interruption of bisphosphonate therapy (drug holiday) predict a difference in fracture outcomes?</u>** **•Data come from extension studies of pivotal trials:** FIT-FLEX: 10 y ALN vs 5 y ALN+ 5 PBO (1099 women) Zoledronic A: 6y Zol PBO vs 3 + 3y PBO (1233 women) Zoledronic A: 9 y Zol vs 6 y Zol + 3 PBO (190 women) Risedronate: no control (PBO) group •Administrative database studies are not useful as they do not provide information on BMD change while off bisphosphonates •Most studies examined **fracture risk** while during a drug holiday comparing to on treatment, rather than **BMD change** to predict fracture risk •Many studies examined BMD and other clinical risk factors at time of entry in the extension phase study as a predictor of fractures as opposed to change in parameter while off Rx **<u>DIRECT EVIDENCE</u>**	

•Only **one** study documents change in BMD over time on fracture risk **while off treatment**: Bauer 2014 (FLEX):

A) Intra-patient BMD CHANGE AND FRACTURE RISK (off treatment): FLEX (437 women on PBO following ALN)

No	Author (year) Sample size (N) Duration	Drug	Sex		Tertile with greatest decrease vs other 2	Risk of Fractures HR (95% CI) 2 year change	Level of bias
			M	W		Any non spine or clinical vertebral	
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Results were similar at 3 years or at lumbar spine BMD (done only at 3 years)

INDIRECT EVIDENCE

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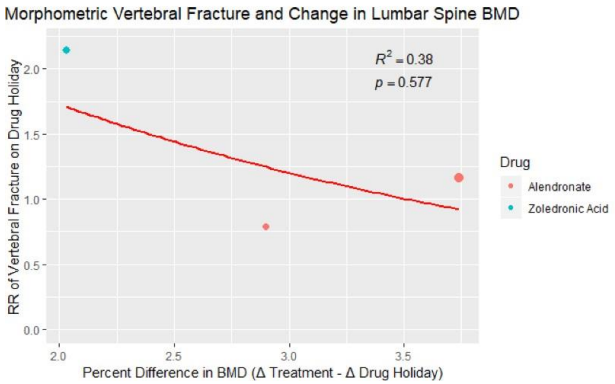
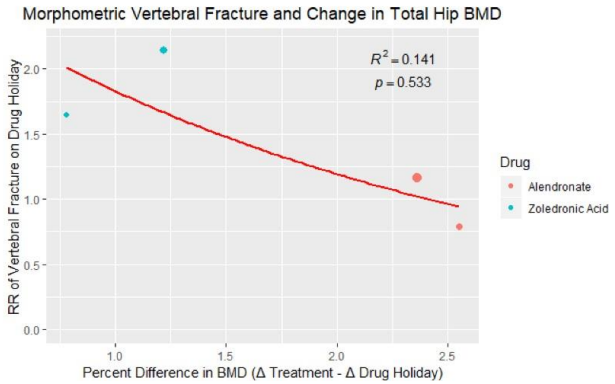
A) BMD CHANGE (OFF TREATMENT-DRUG CONTINUATION VS. DISCONTINUATION-PBO) AND FRACTURE RISK:

No	Author (year) Sample size (N) Duration	Drug	Sex		Difference in BMD, active-placebo (%)			Fracture reduction RR (n fractures)					Level of bias
			M	W	TH	FN	LS	Morphometric Vertebral fracture	Clinical Vertebral fracture	Hip fracture	Nonvertebral fracture	All fracture	
References from Fink 2019, Dennison 2019 and references from our search													
1	**Tonino(2000)** N= 350 Study duration: 7 years; DH after 5 yrs of Rx	ALN		W	-	0.87%	1.33%		RR 0.92 CI (0.40,2.10)	-	RR 0.87 CI (0.40,1.91)	-	High
2	**Bone (2004)** N=994 10 years, DH after 5 yrs	ALN		W	2.55%	3.15%	2.9%	RR 1.40 CI (0.52,3.74)		-	RR 0.81 CI (0.38,1.71)	-	High
3	**Black (2006)** N=1099 6 years	ALN		W	2.36%	1.94%	3.74%	RR 0.86 CI (0.60,1.22)	**RR 0.45** **CI (0.24,0.85)**	RR 1.02 CI (0.51,2.10)	RR 1.00 CI (0.76,1.32)	RR 0.93 CI (0.71,1.21)	High
4	**Black (2012)** N=1233 6 years, DH after 3 yrs	Zoledronic acid		W	1.22%	1.04%	2.03%	**RR 0.47** **CI (0.25,0.87)**		RR 1.17 CI (0.39,3.45)	RR 0.96 CI (0.65,1.42)		High
5	**Black (2015)** N=190 9 years, DH after 6 yrs	Zoledronic acid		W	0.78%	0.06%	-	RR 0.61 CI (0.15,2.61)		-	-	RR 1.11 CI (0.47,2.61)	High

A) Morphometric Vertebral Fractures





Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Very low certainty Direct evidence: Only one extension study - in women with one agent (alendronate) Analysis done by categories (tertiles of change) Event though participants were re-randomised, selection bias remains a possiblity All fractures sites pooled Indirect evidence also fails to support an association between change in BMD and incident fractures while on a drug holiday.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Fracture Outcomes are highly valued by patients. BMD Monitoring is also highly valued by patients It is also promoted by Patient societies (OC, IOF, NOF) Furthermore, patients off treatment (and their clinicians) may be concerned about deteriorating bone strength and value some form of monitoring during this period very highly. In the most recent COPN survey, to the question: **"Provide up to three specific questions you would like to see addressed in the next Canadian Osteoporosis Clinical Practice Guidelines"** there were 88 citations on BMD tests/ response to treatment (out of 193 citations in the theme of Screening-Monitoring).

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No evidence of association between change in BMD (monitoring interval 2 years for hip BMD and 3 years for lumbar spine BMD) and incident fractures while on a drug holiday. However there was found to be an association between greater loss (3%) at the Total Hip, but NOT the Femoral Neck, and incident fractures with a wide confidence interval.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost for the test including technician time and expertise, and radiologist interpretation. However BMD is currently performed in most patients following interruption of pharmacotherapy, even in the absence of evidence; at an interval of less than 2 to 3 years

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	BMD measurement by DXA technology is well established. The cost for the test (including technician time and expertise, and radiologist interpretation) is quite similar in each province. There are limitations in terms of access in rural / remote communities.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Access may be limited in rural or remote regions	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Stakeholders value highly BMD monitoring and this would be acceptable, if effective in predicting fractures while off therapy. Of note, this is current clinical practice in most jurisdictions.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	Feasible to continue proceeding with BMD monitoring- this is current clinical practice	

○ Probably yes ● Yes ○ Varies ○ Don't know	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Very low certainty evidence.
Conditional recommendation
In postmenopausal females and males initiating a drug holiday, we suggest monitoring with DXA-BMD, 3 years after interrupting bisphosphonate therapy.

Three years after *stopping* bisphosphonate therapy (i.e. drug holiday), we suggest repeating BMD testing and clinical assessment of fracture risk to determine the need for resumption of therapy.

Justification

Based on a review of the evidence, we conclude that there is **very low** level evidence to support this recommendation as the evidence comes from one extension study (FLEX) with one agent, in women only. There was a small association (confidence intervals were wide and crossed the null value) between BMD change at the hip while off bisphosphonate treatment and incident fractures.
The indirect evidence did not support an association either.

Nevertheless, BMD monitoring is **highly valued** by patients and very established in clinical practice. It has little undesirable effects (low radiation, non-invasive, short duration for image acquisition). Monitoring may be perceived as even more important since treatment has been withdawn and patients may be very concerned about potential bone loss and increased fracture risk.

Subgroup considerations

No data in men

Implementation considerations

-

Monitoring and evaluation

-

Research priorities

Further research would be useful to help clarify the period of time individuals who are on a drug holiday should stop bisphosphonates for and the parameters for restarting. The ideal length of the discontinuation period may likely vary based on the particular bisphosphonate and factors that affect fracture risk, such as T-scores and age. Other factors that may add to continuation of therapy
include risk factors not included in FRAX but that are important to older adults such as fall risk, frailty, multiple comorbid conditions, and medications that contribute to falls and fractures.
Future studies should include these factors when considering decisions about discontinuation of therapy and the duration of discontinuation.

QUESTION 5B: BONE TURNOVER MARKER

SHOULD WOMEN (MEN) AGED 50 YEARS OR OLDER CURRENTLY ON A BISPHOSPHONATE INTERRUPTION OR HIATUS (BH) BEING MONITORED WITH REPEAT DXA, FRACTURE RISK SCORE WITH DXA (E.G., FRAX, CAROC), BONE TURNOVER MARKERS (BTM) VERSUS CLINICALLY (NO SPECIFIC TESTING)?

Should BTM change while on drug holiday vs. BTM stability be used for predicting a change in fracture outcome?	
POPULATION:	predicting a change in fracture outcome
INTERVENTION:	BTM change while on drug holiday
COMPARISON:	BTM stability
MAIN OUTCOMES:	FLEX- Risk of Any non-spine or clinical vertebral fractures and change in NTx (Tertile with greatest increase vs the other 2). ; FLEX- Risk of Any non-spine or clinical vertebral fractures and change in BAP (Tertile with greatest increase vs the other 2); FLEX- Risk of Any non-spine or clinical vertebral fractures and change in NTX (Tertile with greatest increase vs other 2); Flex- Risk of Any non-spine or clinical vertebral vertebral fractures and change in BAP (Tertile with greatest change vs other 2);
SETTING:	during a bisphosphonate holiday
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes **Osteoporosis** poses an immense burden to the society in terms of morbidity, mortality and financial **cost**. To reduce this burden, it is essential to accurately assess the individual patient's fracture risk and, where indicated, to initiate appropriate treatment that reduces fracture probability. Current **monitoring** approaches include utilization of bone mineral density measurement by Dual Energy X-ray Absorptiometry (DXA) and bone turnover markers (formation and resorption). Bisphosphonate interruption (drug holiday) after 3 to 5 years are now almost standard of care in those who are not at very high risk for fractures. Monitoring while during drug interruption (drug holiday) is a very important issue to patients, clinicians and policy makers. Already most patients receive BMD to monitor response **OFF** therapy often with intervals as short as 12 months. BTMs as monitoring tools are less frequently used in Canada. FRAX is not used to monitor treatment, as it is unknown if it is responsive to treatment.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	•**Data come from extension studies of pivotal trials:** FIT-FLEX: 10 y ALN vs 5 y ALN+ 5 PBO (1099 women) Zoledronic A: 6y Zol PBO vs 3 + 3y PBO (1233 women) Zoledronic A: 9 y Zol vs 6 y Zol + 3 PBO (190 women) Risedronate: no control (PBO) group

•Administrative database studies are not useful as they do not provide information on BTMs change while off bisphosphonates
•Studies examined BTMs and other clinical risk factors at time of entry in the extension phase study as a predictor of fractures as opposed to change in parameter while off treatment as a predictor of fracture

DIRECT EVIDENCE

•Only **one** study documented change in BTMs over time on fracture risk **while off treatment**: Bauer 2014 (FLEX, alendronate vs pbo)
There was **no association** between BTM change and fracture risk

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without BTM change while on drug holiday	With BTM change while on drug holiday	Difference		
FLEX- Risk of Any non-spine or clinical vertebral fractures and change in NTx (Tertile with greatest increase vs the other 2). (Any non vert and clinical spine) follow-up: mean 1 years № of participants: (1 observational study)	**HR 1.14** (0.70 to 1.86)	Study population			⨁◯◯◯ Very low[a,b]	
		0.0%	**NaN%** (NaN to NaN)	-- (-- to --)		
FLEX- Risk of Any non-spine or clinical vertebral fractures and change in BAP (Tertile with greatest increase vs the other 2) (Any non vert and clinical spine) follow-up: mean 1 years № of participants: (1 observational study)	**HR 1.03** (0.63 to 1.67)	Study population			⨁◯◯◯ Very low[a,b]	
		0.0%	**NaN%** (NaN to NaN)	-- (-- to --)		
FLEX- Risk of Any non-spine or clinical vertebral fractures and change in NTX (Tertile with greatest increase vs other 2) (Any non-spine clinical Fx) follow-up: mean 3 years № of participants: (1 observational study)	**HR 1.02** (0.55 to 1.91)	Low			⨁◯◯◯ Very low[a,c]	
		0.0%	**NaN%** (NaN to NaN)	-- (-- to --)		
Flex- Risk of Any non-spine or clinical vertebral vertebral fractures and change in BAP (Tertile with greatest change vs other 2) (Any non-spine and clinical vert Fx) follow-up: mean 3 years № of participants: (1 observational study)	**HR 0.79** (0.41 to 1.50)	Study population			⨁◯◯◯ Very low[a,c]	
		0.0%	**NaN%** (NaN to NaN)	-- (-- to --)		

a. selection bias
b. imprecise data- few numbers of Fractures 2 years N=70
c. imprecise data- very few fractures (N=57) at 3 years

Intra-patient BTM difference and Fracture Risk Reduction Values (off treatment)

No	Author (year) Sample size (N) Duration	Drug	Sex		Tertile with greatest increase vs other 2	Risk of Fractures HR (95% CI) 1 year change	Level of bias
			M	W		Any non spine or clinical vertebral	
1	**Bauer (2014)** N= 1099 **437 on PBO** Study duration: 7 years; DH after 5 yrs of Rx	ALN		W	NTx/Cr BAP	**1.14 (0.70-1.86)** **1.03 (0.63-1.67)**	HIGH

Results were similar at 3 years, or with a >30% increase in the BTMs

INDIRECT EVIDENCE

we did not analyse indirect evidence in view of the limitations regarding BTMs already documented in Question 4
We did not identify any citations as to whether BTM change off therapy was associated with change in treatment.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

•Data regarding drug holiday come from extension studies of pivotal trials:
FIT-FLEX: 10 y ALN vs 5 y ALN+ 5 PBO (1099 women)
Zoledronic A: 6y Zol PBO vs 3 + 3y PBO (1233 women)
Zoledronic A: 9 y Zol vs 6 y Zol + 3 PBO (190 women)
Risedronate: no control (PBO) group

•Administrative database studies are not useful as they do not provide information on BTMs change while off bisphosphonates
•Many studies examined BTMs and other clinical risk factors at time of entry in the extension phase study as a predictor of fractures as opposed to change in parameter while off Rx

DIRECT EVIDENCE

•Only **one** study documents change in BTMs over time on fracture risk **while off treatment**: Bauer 2014 (FLEX alendronate vs pbo):
There was **no association** between BTM change and fracture risk

Intra-patient BTM difference and Fracture Risk Reduction Values (off treatment)

No	Author (year) Sample size (N) Duration	Drug	Sex		Tertile with greatest increase vs other 2	Risk of Fractures HR (95% CI) 1 year change	Level of bias
			M	W		Any non spine or clinical vertebral	
1	**Bauer (2014)** N= 1099 **437 on PBO** Study duration: 7 years; DH after 5 yrs of Rx	ALN		W	NTx/Cr BAP	**1.14 (0.70-1.86)** **1.03 (0.63-1.67)**	HIGH

Results were similar at 3 years, or with a >30% increase in the BTMs

INDIRECT EVIDENCE

we did not analyse indirect evidence in view of the limitations regariding BTMs already documented in Question 4

We did not identify any citations as to whether BTM change off therapy was associated with change in treatment.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	very low certainty Direct evidence: Only one extension study - in women with one agent (alendronate) Analysis done by categories (tertiles of change) Selection bias are present, even though patients are re-randomized All fractures sites pooled	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or	Fracture Outcomes are highly valued by patients. Monitoring is also highly valued by patients IOF and Bone Health and Osteoporosis Foundation (formely NOF) recommend use of BTMs in the monitoring of adherence to therapy (not to predict fracture reduction).	

variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Furthermore, patients off treatment (and their healthcare providers) are concerned about deteriorating bone strength and would likely value some form of monitoring very highly. In the most recent COPN survey, to the question: **"Provide up to three specific questions you would like to see addressed in the next Canadian Osteoporosis Clinical Practice Guidelines"** there were 88 citations on BMD tests/ response to treatment (out of 193 citations in the theme of Screening-Monitoring).

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There was no association between BTM changes and fracture incidence while on bisphosphonate interruption (holiday) BTMs' clinical value for monitoring is limited by inadequate appreciation of the sources of variability, by limited data for comparison of treatments using the same BTM and by inadequate quality control.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Costs associated with the routine measurement of BTMs for monitoring of patients at this time, in view, for example of the issue of reproducibility of BTM levels measured by commercial laboratories, the thresholds to effect a change in therapy, etc. would be moderate to high .	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ● Moderate ○ High ○ No included studies	One may consider an alternative algorithm be put in place whereby we would monitor patients with BTMs instead of using BMD. Costs might then be mitigated. However, no data have looked at the effectiveness of such an approach- so this would be speculative at this point.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Currently many centres do not have access to BTM measurements and/or they are not reimbursed by provincial health insurance programs. So equity would be reduced on the basis of differential availabity and reimbursement between provinces or private insurance programs.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	This would likely be acceptable to patients and possibly to clinicians if BTMs were wideley available and results reliable, and if they became familiar with their interpretation.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Costs, type of assay, expertise in interpretation. At this time, it would be difficult to implement in routine primary care.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	**No**	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

Very low level certainty evidence
We suggest against the use of bone turnover markers for monitoring postmenopausal females and males following temporary discontinuation of bisphosphonates

Related recommendation(s)

1. Should BMD change while on bisphosphonate interruption vs. BMD stability be used for predicting fracture outcome?
Very low certainty evidence.
Conditional recommendation
In indiviudals initiating a drug holiday, we suggest monitoring with DXA-BMD, 3 years after interrupting bisphosphonate therapy.

Justification

Based on a review of the evidence, we conclude that there is **very low** level evidence to support this recommendation as the evidence comes from one extension study (FLEX) with one agent, in women only. There was no association (confidence intervals were wide and crossed the null value) between BTM change while off bisphosphonate treatment and incident fractures.
There are **many limitations** with BTM measurements currently, including lack of standard thresholds, commercial assays variability, clinical algorithms -intervals at which they should be measured, how frequently, etc-. Nevertheless, monitoring is **highly valued** by patients and very established in clinical practice. Monitoring may be perceived as even more important since treatment has been withdawn and patients may be very concerned about potential bone loss and increased fracture risk.

Subgroup considerations

no data in men

Implementation considerations

-

Monitoring and evaluation

-

Research priorities

Further research would be useful to help clarify the period of time individuals who are on a drug holiday should stop bisphosphonates for and the parameters for restarting. The ideal length of the discontinuation period may likely vary based on the particular bisphosphonate and factors that affect fracture risk, such as T-scores and age. Other factors that may add to continuation of therapy include risk factors not included in FRAX but that are important to older adults such as fall risk, frailty, multiple comorbid conditions, and medications that contribute to falls and fractures. Future studies should include these factors when considering decisions about discontinuation of therapy and the duration of discontinuation.

QUESTION 6: SHOULD FRACTURE LIAISON SERVICES (FLS) BE RECOMMENDED TO IMPROVE POST FRACTURE CARE/ FRACTURE RISK REDUCTION VERSUS USUAL CARE?

Should FLS vs. Std care be used for OP?	
POPULATION:	OP
INTERVENTION:	FLS
COMPARISON:	Std care
MAIN OUTCOMES:	BMD testing; Treatment Initiation rate; Adherence; Re-fracture; Mortality; Adherence; Re-fracture; Mortality;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

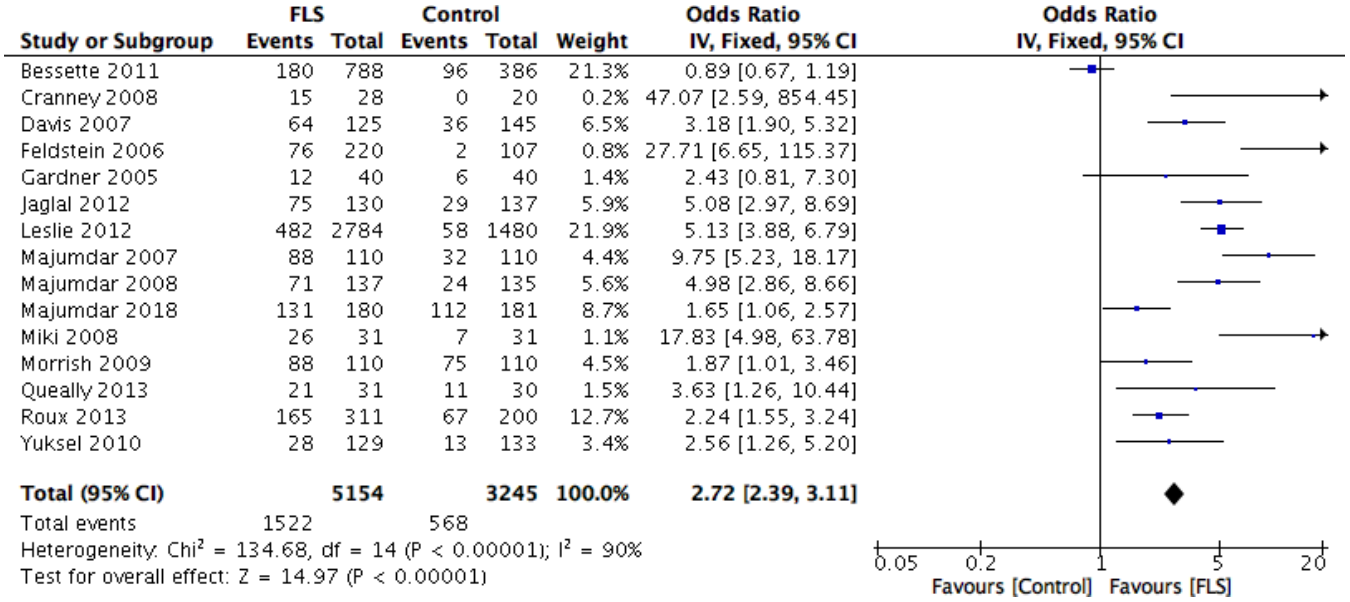
Problem
Is the problem a priority?

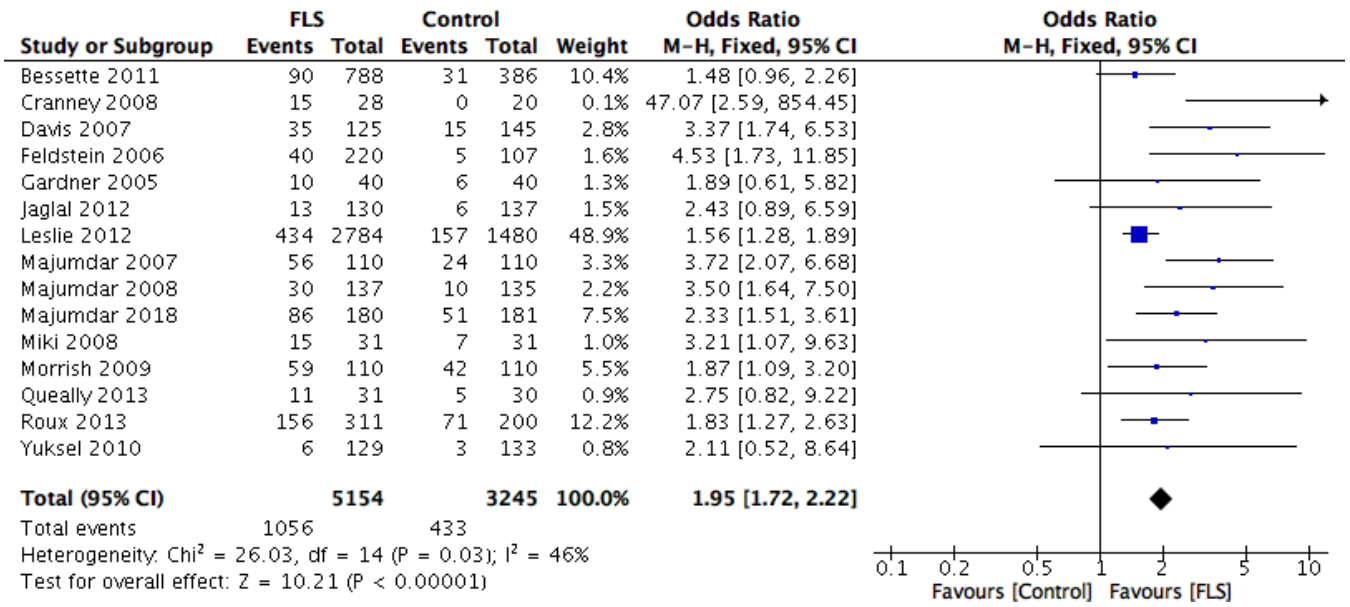
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The provision of FLS services is currently recommended in guidelines for the prophylaxis of secondary bone fractures issued by the American Society for Bone and Mineral Research (ASBMR) [9] and European League Against Rheumatism (EULAR)/European Federation of National Associations of Orthopaedics and Traumatology (EFFORT). We have identified a recent meta analysis.	

Table 1
Summary results from meta-analysis of RCTs and controlled observational studies.[a]

Outcome	Study design	Number of studies	Study/follow-up duration (months)	Absolute risk difference, 95% CI (intervention vs control)	Unweighted averages (intervention vs control)		Statistical heterogeneity (I^2), %	NNT
BMD testing	RCTs	13	3–13	0.23 (0.16 to 0.29)*	–	–	90	4
	Controlled observational	24	1–26	0.24 (0.15 to 0.33)	–	–	96.9	4
	Total	**37**	**3–26**	**0.24 (0.18 to 0.29)**	**23.5%**	**48.0%**	**96.1**	**4**
Treatment initiation	RCTs	14	3–12	0.14 (0.09 to 0.18)*	–	–	85.6	7
	Controlled observational	32	3–72	0.22 (0.16 to 0.28)	–	–	96.4	5
	Total	**46**	**3–72**	**0.20 (0.16 to 0.25)***	**17.2%**	**38.0%**	**95.8**	**5**
Adherence	RCTs	2	6–24	0.14 (−0.06 to 0.35)	–	–	69.6	–
	Controlled observational	7	3–48	0.24 (0.13 to 0.35)	–	–	79.8	4
	Total	**9**	**6–48**	**0.22 (0.13 to 0.31)***	**34.1%**	**57.0%**	**75.8**	**5**
Re-fracture	RCTs	2	6	−0.004 (−0.04 to 0.03)	–	–	0	–
	Controlled observational	9	6–72	−0.06 (−0.09 to −0.03)	–	–	92.8	–
	Total	**11**	**6–72**	**−0.05 (−0.08 to −0.03)***	**13.4%**	**6.4%**	**91.1**	**20**
Mortality	RCTs	4	6–12	−0.02 (−0.06 to 0.03)	–	–	75.8	–
	Controlled observational	11	12–72	−0.04 (−0.07 to −0.01)	–	–	83	25
	Total	**15**	**6–72**	**−0.03 (−0.05 to −0.01)***	**15.8%**	**10.4%**	**81.2**	**33**

BMD, bone mineral density; CI, confidence interval; n/a, not applicable; NNT, number needed to treat; RCT, randomised controlled trial.
[a] Random-effects model.
* $p \leq 0.05$.





Study or Subgroup	FLS Events	FLS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bessette 2011	90	788	31	386	10.4%	1.48 [0.96, 2.26]
Cranney 2008	15	28	0	20	0.1%	47.07 [2.59, 854.45]
Davis 2007	35	125	15	145	2.8%	3.37 [1.74, 6.53]
Feldstein 2006	40	220	5	107	1.6%	4.53 [1.73, 11.85]
Gardner 2005	10	40	6	40	1.3%	1.89 [0.61, 5.82]
Jaglal 2012	13	130	6	137	1.5%	2.43 [0.89, 6.59]
Leslie 2012	434	2784	157	1480	48.9%	1.56 [1.28, 1.89]
Majumdar 2007	56	110	24	110	3.3%	3.72 [2.07, 6.68]
Majumdar 2008	30	137	10	135	2.2%	3.50 [1.64, 7.50]
Majumdar 2018	86	180	51	181	7.5%	2.33 [1.51, 3.61]
Miki 2008	15	31	7	31	1.0%	3.21 [1.07, 9.63]
Morrish 2009	59	110	42	110	5.5%	1.87 [1.09, 3.20]
Queally 2013	11	31	5	30	0.9%	2.75 [0.82, 9.22]
Roux 2013	156	311	71	200	12.2%	1.83 [1.27, 2.63]
Yuksel 2010	6	129	3	133	0.8%	2.11 [0.52, 8.64]
Total (95% CI)		**5154**		**3245**	**100.0%**	**1.95 [1.72, 2.22]**
Total events	1056		433			

Heterogeneity: Chi² = 26.03, df = 14 (P = 0.03); I² = 46%
Test for overall effect: Z = 10.21 (P < 0.00001)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	•After pooling 15 RCTs (n=3245) comparing FLS VS. Control (1) FLS improve **BMD testing** (OR=3.82 (2.4, 6.0) FLS improve **treatment initiation** (OR=2.3 (1.8,2.8) No differences in the types of FLS (Type A, B and C) •Refracture 2 RCTs (-0.004, -0.04 to +0.03) 9 observational studies (-0.06, -0.09 to -0.03) •Mortality 4 RCTs (-0.02, -0.06 to +0.03) 9 observational studies (-0.04, -0.07 to -0.01) •Adherence 2 RCTs (+0.14, -0.06 to +0.35) 7 observational studies (+0.24, +0.13 to +0.35)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	There was no undesirable effect reported in Wu et al. see evidence in box 1

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	There high certainty evidence that FLS improve identification and treatment initation in adults who present with a recent fracture. The certainty of evidence is lower for re-fracture and mortality.	

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
BMD testing (follow-up: range 3 months to 13 months; assessed with: Number of BMD test)							
15	randomised trials	not serious[a]	serious[b]	not serious	not serious	strong association	⨁⨁⨁⨁ High
Treatment Initiation rate (follow-up: range 3 months to 12 months; assessed with: number of patients initiated treatment)							
15	randomised trials	not serious[a]	serious[b]	not serious	not serious	strong association	⨁⨁⨁⨁ High
Adherence (follow-up: range 6 months to 24 months; assessed with: Adherence Questionnaire)							
2	randomised trials	very serious[d]	not serious	not serious	serious[e]	none	⨁◯◯◯ Very low
Re-fracture (follow-up: mean 6 months)							
2	randomised trials	serious[f]	not serious	not serious	very serious[e]	none	⨁◯◯◯ Very low
Mortality (follow-up: range 6 months to 12 months)							
2	randomised trials	very serious[g]	not serious	not serious	very serious[e]	none	⨁◯◯◯ Very low
Adherence (follow-up: range 3 months to 48 months)							
7	observational studies	not serious	serious[b]	not serious	serious[e]	none	⨁◯◯◯ Very low
Re-fracture (follow-up: range 6 months to 72 months)							
9	observational studies	not serious	serious[b]	not serious	not serious[e]	none	⨁◯◯◯ Very low
Mortality (follow-up: range 12 months to 72 months)							
11	observational studies	not serious	serious[b]	not serious	serious[e]	none	⨁◯◯◯ Very low

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes of BMD testing, treatment adherence and initiation are highly valued by patients and clinicians, Fractures and mortality are highly valued. When we survey patients, these outcomes were generally highly valued.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The desirable effect outweigh the undesirable effects, even when costs are considered.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	A systematic review (Wu et al 2017) summarized 23 studies of FLS economic analysis. it was shown that FLS is cost-effective. The amount of cost saving is different between studies.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Resources are required to implement FLS in all jursidictions	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies	A systematic review (Wu et al 2017) summarized 23 studies of FLS economic analysis. it was shown that FLS is cost-effective.	

○ No included studies	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No evidence was found regarding the impact of FLS on equity. Although if implemented across jurisdictions, it would probably improve equity	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	FLS appear to be acceptsble, considreing the number of FLS centres across the world	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	FLS appear to be feasible, considreing the number of observational and RCTs studies conducted.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

We recommend availability of a Fracture Liaison Service to improve identification and treatment of osteoporosis in patients over age 50 with fracture (strong recommendation, high certainty evidence)

Justification

Subgroup considerations

Implementation considerations

Monitoring and evaluation

INITIATING TREATMENT

QUESTION 1A: FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF FRACTURES (TO DEFINE), SHOULD PHARMACOTHERAPY* BE RECOMMENDED?

QUESTION 1B: SHOULD ONE PHARMACOTHERAPY AGENT* VERSUS ANOTHER BE RECOMMENDED AS THE INITIAL TREATMENT CHOICE FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINED BY SUBGROUPS)?
*USING BISPHOSPHONATES (ALENDRONATE, RISEDRONATE, ZOLEDRONIC ACID, ETIDRONATE), DENOSUMAB, TERIPARATIDE, ROMOSOZUMAB, RALOXIFENE (WOMEN ONLY) OR ESTROGEN (WOMEN ONLY)

Should one pharmacotherapy agent vs. another be used for individuals initiating pharmacotherapy ?	
POPULATION:	Patients initiating pharmacotherapy
INTERVENTION:	Pharmacotherapy agent (e.g., bisphosphonates)
COMPARISON:	Estrogen therapy, Denosumab, Teriparatide, Romosozumab, Etidronate or Raloxifene
MAIN OUTCOMES:	Fractures (hip, non-vertebral, vertebral), adverse events (e.g., gastrointestinal, cardiovascular, osteonecrosis of the jaw, atypical femur fracture)
SETTING:	Outpatient
PERSPECTIVE:	Population

Desirable effects/benefit	
	We searched for previously published systematic reviews using Epistemonikos and found a network meta-analysis (Barrionuevo 2019). Calculations for benefits used the Risk Ratio from the analysis and were applied to risks with no medication (none) for hip, non-vertebral, and vertebral fractures at 3 years per 1000 people. The minimum threshold for benefit is a reduction of ≥3 hip fractures (dark yellow); ≥14 non-vertebral fractures (dark green); and, ≥14 vertebral fractures (dark blue). Etidronate was not included in the analysis and therefore evidence from Wells 2008 was used. Evidence for effects in men was available from Nayak 2017. The analyses from Nayak 2017 (when available) showed similar effects for fractures and therefore the guideline group agreed that the effects from Barrionuevo 2019 would likely apply to men. Certainty of evidence rating down: * Serious concern about imprecision; ** Very serious concern about imprecision; † Serious concern about risk of bias References Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis. J Clin Endocrinol Metab. 2019;104(5):1623-30. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004523. Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2017;65(3):490-5.

	Alendronate	Risedronate	Zoledronate	Estrogen therapy	Raloxifene	Etidronate	Denosumab	Teriparatide	Romo-sozumab	None
Hip	0.61 (0.42,0.90)	0.73 (0.58,0.92)	0.60 (0.45,0.81)	0.72 (0.53,0.98)	0.91 (0.71,1.17)	No difference	0.56 (0.35,0.90)	0.64 (0.25,1.68)	0.44 (0.24,0.79)	
	-4	-3	-4	-3	-1	0	-4	-4	-6 (-8 to -2)	10
	H	H	H	M†	M*	L	H	M*	Moderate	
Non-vertebral	0.84 (0.74,0.94)	0.78 (0.68,0.89)	0.79 (0.67,0.94)	0.78 (0.68,0.89)	0.94 (0.85,1.05)	No difference	0.80 (0.67,0.96)	0.62 (0.47,0.80)	0.67 (0.53,0.86)	
	-8	-11	-11	-11	-3	0	-10	-19	-17	50
	H	H	H	M†	M*	L	H	H	H	
Vertebral (ALL)	0.57 (0.45,0.71)	0.61 (0.48,0.78)	0.38 (0.25,0.58)	0.65 (0.46,0.92)	0.59 (0.46,0.76)	0.59 (0.36, 0.96)	0.32 (0.22,0.45)	0.27 (0.19,0.38)	0.33 (0.22,0.49)	
	-22	-20	-31	-18	-21	-21	-34	-37	-34	50
	H	H	H	M†	H	L	H	H	H	

	Alendronate	Risedronate	Zoledronate	Estrogen therapy	Raloxifene	Etidronate	Denosumab	Teriparatide	Romo-sozumab	None
Size of benefits	Moderate (likely trivial effect if FN T-score -2.0 to -1.6 and no previous fracture)	Moderate	Moderate	Moderate	Small	Small	Moderate (FN> -2.5); moderate (FN T-score <-2.5 greater reduction non-vertebral and hip fractures if >75)	Moderate (at 18-24 months)	Moderate (at 12 months)	
Undesirable effects/harms	Evidence for harms was from the AHRQ report (Crandall 2012, Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report. Comparative Effectiveness Review No. 53. (Prepared by Southern California Evidence-based Practice Center under Contract No. HHSA-290-2007-10062-I.). Rockville, MD: Agency for Healthcare Research and Quality. When not available from the AHRQ report, results from individual studies for each medication are presented with references.									
Serious adverse events	adverse events leading to hospitalisation : 29% (alendronate) vs 27% placebo	serious GI events: OR 0.94 (0.75 to 1.19)	serious adverse events: 40% (Zoledronate) vs 44.3 % (placebo) Immediate adverse events with infusion	*Estrogen plus progestin:* invasive breast cancer HR 1.26 (1.00, 1.59) *Estrogen only* invasive breast cancer HR 0.77 (0.59, 1.01) colorectal cancer HR 1.08 (0.75, 1.55)	serious adverse events: 23% (raloxifene) vs 25% (placebo)	Similar to placebo (Wells 2008)	serious adverse events: 17.8% (denosumab) vs 10.9% (placebo)	serious GI events: none reported	adverse events: RR 1.00, 95% CI 0.98-1.02 (Liu 2018)	

	Alendronate	Risedronate	Zoledronate	Estrogen therapy	Raloxifene	Etidronate	Denosumab	Teriparatide	Romo-sozumab	None
Other adverse events	upper GI tract: 47.5% (alendronate) vs 46.2% (placebo)	musculoskeletal events: OR 0.77 (0.45 to 1.3)		*Estrogen plus progestin:* DVT: HR 2.07 (1.49, 2.87) Pulmonary embolism HR 2.13 (1.39, 3.25) *Estrogen only* DVT HR 1.47 (1.04, 2.08) pulmonary embolism HR 1.34 (0.87, 2.06)	DVT: 4 to 8 years f/u; RR 2.8 (1.3 to 5.9) to RR 3.1 (1.4 to 6.9) Pulmonary embolism: RR 4.5 (1.1 to 19.5)		Rapid bone loss below baseline when stopping or delayed dose)	Bone loss to baseline when stopping Cancer: OR 0.49 (0.27, 0.90); RD -0.018 (-0.034, -0.003) Transient hypercalcemia OR 12.9 (10.49, 16.00)	Bone loss to baseline when stopping	
Cardiovascular events	Atrial fibrillation: 1.3% (alendronate) vs 1.0% (placebo)	Serious Atrial Fibrillation: OR 1.59 (0.61 to 3.75) AHRQ 2012	CVD: 5.3% (Zoledronate) vs 6.9% (placebo)	*Estrogen plus progestin:* composite outcome of cardiovascular disease HR 1.22 (1.09, 1.36) *Estrogen only* composite outcome of cardiovascular disease HR 1.12 (1.01, 1.24)	CVD: 'no differences'; Atrial fibrillation: OR 0.82 (0.6 to 1.13)		CVD: 1 stroke in denosumab group vs 0 (placebo)		serious cardiovascular adverse events: 50 patients (2.5%) romosozumab group and 38 (1.9%) alendronate (Saag 2017)	
Size of harms	Trivial harms	Trivial harms	Trivial harms	Small harms	Small harms	Trivial harms	Small to moderate harms	Trivial to Small harms	Small harms	
Costs	NEGLIGIBLE	NEGLIGIBLE	NEGLIGIBLE TO SMALL	NEGLIGIBLE TO SMALL	NEGLIGIBLE	NEGLIGIBLE	SMALL TO MODERATE	LARGE	LARGE	

	Alendronate	Risedronate	Zoledronate	Estrogen therapy	Raloxifene	Etidronate	Denosumab	Teriparatide	Romo-sozumab	None
			(generic is lower)	(brand name or transdermal forms more costly)				(may be generic soon and price may lower)		
Equity	YES	YES	AVAILABLE, NOT REIMBURSED ON MOST PROVINCIAL PLANS	YES, MAY NOT BE COVERED, BUT OPTIONS FOR PRICES	YES	MAY NOT BE AVAILABLE	YES, MAY NOT BE COVERED	MINIMAL COVERAGE; AND MEET CRITERIA	UNKNOWN	
Acceptability	YES, SOME PERCEIVED BURDEN - WAIT FOR BREAKFAST, ONCE A WEEK DOSING	YES, SOME PERCEIVED BURDEN - WAIT FOR BREAKFAST, ONCE A WEEK DOSING	ACCEPTABLE IV ROUTE AND LESS FREQUENCY; MAY BE LESS PRESCRIBED	MANY OPTIONS TO TAKE (PILL, PATCH..)	TAKE EVERYDAY, NO BURDEN TO TAKE	YES	CONCERN IF HARMS WHEN DOSE SKIPPED OR NEED TO DISCONTINUE (injections are not a burden)	BURDEN TO CARRY DRUGS; DAILY INJECTION is very important burden	PROBABLY, BUT NO EXPERIENCE for clinicians	
Feasibility	YES	YES	YES, BUT INFUSION CLINICS may not be easily accessible, Need to monitor pre and post dose (e.g. for hypocal-caemia and renal function	YES, MAY NOT BE COVERED BUT IS AFFORDABLE, BUT LARGE DIFFERENCES IN COST DEPENDING ON CHOSEN THERAPY	YES,	VARIES – need special access to receive a drug other than etidronate (e.g., clinically or radiologically confirmed fracture in BC; or SK failed etidronate YK - coverage if >65 years	YES, CAN PROVIDE SUBCUTANEOUSLY IN OFFICE Need to monitor more (e.g., hypocal-caemia); need to ensure dosing every 6 months	INJECTION EVERY DAY	MONTHLY INJECTION (AT OFFICE); inconvenient but can be done indepen-dently; Only approved up to 12 months	

RECOMMENDATION

For individuals meeting criteria for initiation, we recommend bisphosphonates (alendronate, risedronate or zoledronic acid) **(GRADE: strong- high certainty evidence for females and moderate certainty evidence for males).**

Remarks: Oral bisphosphonates may be preferred since drug coverage, costs and access to an infusion centre may be barriers to zoledronic acid.

For postmenopausal females <60 years old or within 10 years of menopause initiating pharmacotherapy who prioritize alleviation of important menopausal symptoms, we suggest menopausal hormone therapy (MHT) as an alternative option to bisphosphonate therapy **(GRADE: conditional- moderate certainty evidence).**
Remarks: The choice will also depend on individualized risks to MHT which consists of an estrogen dose equivalent to conjugated equine estrogens of 0.625 mg daily (plus progestogen in women who have a uterus).

For individuals meeting criteria for initiation of pharmacotherapy who have contraindications or important intolerance or barriers to bisphosphonates, we suggest denosumab.
(GRADE: conditional- high certainty evidence for females and moderate certainty evidence for males).
Remarks: Despite the benefits of denosumab, a careful assessment of indications is required due to risk of rapid bone loss and increased vertebral fractures with delayed dosing or discontinuation of denosumab. It is important to communicate the need to commit to long-term therapy and the need to transition to alternative antiresorptive therapy if discontinuing denosumab. Denosumab may be preferred when there is a high burden of oral medications, gastrointestinal intolerance or contraindication to oral bisphosphonates or barriers to accessing IV zoledronic acid.

For individuals meeting criteria for initiation of pharmacotherapy who have had a recent severe vertebral fracture, or more than one vertebral fracture, AND a T-score ≤-2.5, we suggest seeking advice) from a consultant with expertise in osteoporosis about anabolic therapy (teriparatide or romosozumab) (**GRADE: conditional- high certainty evidence for females and moderate certainty evidence for males**).
Remark: Recent fracture is defined as occurring within the past 2 years, and *severe vertebral fracture as vertebral body height loss of > 40%. Clinicians may seek advice from radiologists to clarify the degree of severity of the vertebral fracture. The choice of anabolic therapy may depend on affordability and feasibility of injection schedule.

For postmenopausal females initiating pharmacotherapy who have contraindications or important intolerance to, or who choose not to take other suggested therapies, we suggest raloxifene rather than no treatment.(GRADE: conditional – moderate certainty evidence)
Remark: Raloxifene should only be used in those who are not at high risk of venous thromboembolism.

JUSTIFICATION

Bisphosphonates: There are moderate benefits and trivial harms. Costs are negligible with oral bisphosphonates, which are also acceptable and feasible. However, costs may be greater with IV zolendronic acid, which may not be reimbursed and infusion clinics may not be easily accessible.

Etidronate and Raloxifene: There are likely small benefits and small to trivial harms. Costs are negligible, but etidronate may not be available in some provinces or may be the first option to prescribe before receiving other medications. Etidronate has now been cancelled by all generic manufacturers in Canada.

Estrogen therapy: There are likely moderate benefits, but small harms. Costs are generally negligible depending on form, but may not be covered by some insurances.

Denosumab: There are moderate benefits and small to moderate harms, and can result in rapid bone loss and risk of vertebral fracture when stopping or when a dose is delayed. Denosumab may have small to moderate costs, and may not be covered by some insurances. It needs to be provided in office or other facility and requires more monitoring than bisphosphonates.

Teriparatide and Romosozumab: There are likely moderate benefits, and trivial to small (with teriparatide) to small harms (with romosozumab). Teriparatide needs to be injected daily and costs are large. Romozosumab needs to be injected monthly,but costs are also large. When stopping teriparatide or romozosumab bone loss to baseline levels can occur (therefore follow-up medications are necessary).

DURATION OF ORAL BISPHOSPHONATES

QUESTION 2: SHOULD LONGER DURATION OF ORAL BISPHOSPHONATES VERSUS SHORTER DURATION BE RECOMMENDED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINE BY SUBGROUPS)?

QUESTION 5: SHOULD A CHANGE IN PHARMACOTHERAPY BE RECOMMENDED WHEN NEW FRACTURE(S) AND/OR UNEXPECTED BONE LOSS OCCURS WHILE ON EFFECTIVE TREATMENT VERSUS NO CHANGE IN PHARMACOTHERAPY, FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINE BY SUBGROUPS)?

Should longer duration versus shorter be used for individuals taking oral bisphosphonates?	
POPULATION:	individuals taking oral bisphosphonates
INTERVENTION:	Longer duration of therapy
COMPARISON:	Shorter duration
MAIN OUTCOMES:	Hip fracture, vertebral fracture, non-vertebral fracture, adverse events (e.g., atypical femoral fractures, osteonecrosis of the jaw)
SETTING:	Outpatient
PERSPECTIVE:	Population

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We used a systematic review of randomised and non-randomised studies published by AHRQ in April 2019 (search up to October 2018). **Reference**	The Guideline panel identified the differences that would represent a moderate benefit. A moderate benefit for total factures is 68 fewer, however

Fink HA, MacDonald R, Forte ML, Rosebush CE, Ensrud KE, Schousboe JT, Nelson VA, Ullman K, Butler M, Olson CM, Taylor BC, Brasure M, Wilt TJ. Long-Term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention: A Systematic Review. Comparative Effectiveness Review No. 218. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-00008-I) AHRQ Publication No. 19-EHC016-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2019.

ALENDRONATE

Evidence for alendronate is from an extended randomised controlled trial (Black 2006) of 5 years with alendronate followed by placebo or continued for 10 years. Results are presented for women with T score <-1.6 and T score <-2.5.

Additional analyses in subgroups:

Analyses were also conducted to determine if results would be different for subgroups of patients. For lower BMD at the femoral neck (FN) and history of prior fracture and effects on nonvertebral and vertebral fractures, all differences were not significant.

Reference

Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR; FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006 Dec 27;296(24):2927-38.

Outcomes	With therapy of up to 3-5 years	With longer therapy	Difference	Relative effect (95% CI)	Certainty of the evidence
clinical fractures follow up: 10 years	255 per 1,000	**237 per 1,000** (181 to 309)	**18 fewer per 1,000** (74 fewer to 54 more)	**RR 0.93** (0.71 to 1.21)	⨁⨁⨁◯ MODERATE[a,b]
non-vertebral fractures follow up: 10 years	135 per 1,000	**135 per 1,000** (103 to 178)	**0 fewer per 1,000** (32 fewer to 43 more)	**RR 1.00** (0.76 to 1.32)	⨁⨁⨁◯ MODERATE[b]
hip fracture follow up: 10 years	25 per 1,000	**26 per 1,000** (13 to 53)	**1 more per 1,000** (12 fewer to 28 more)	**RR 1.02** (0.51 to 2.10)	⨁⨁◯◯ LOW[b]
vertebral fracture assessed with: clinical only follow up: 10 years	40 per 1,000	**18 per 1,000** (10 to 34)	**22 fewer per 1,000** (30 fewer to 6 fewer)	**RR 0.45** (0.24 to 0.85)	⨁⨁⨁◯ MODERATE[b]
vertebral fracture assessed with: radiological follow up: 10 years	120 per 1,000	**103 per 1,000** (72 to 146)	**17 fewer per 1,000** (48 fewer to 26 more)	**RR 0.86** (0.60 to 1.22)	⨁⨁◯◯ LOW[b]

we found 18 fewer with longer treatment; for non-vertebral we found no difference; and for hip fractures we found little to no difference. For vertebral fractures (clinical only) 14 fewer is important and we found 22 fewer - an important reduction; and for radiologically confirmed 41 fewer is important, but we found 17 fewer - a small reduction.

The guideline panel agreed that there do not seem to be different benefits in different subgroups (e.g., people with lower BMD or who had a prior fracture).

Benefits for risedronate are uncertain given small numbers; but it is unlikely risedronate would be more or less beneficial than alendronate. In addition, harms for risedronate were not reported, and likely harms would be similar to alendronate.

Data for etidronate was available for only up to 4 years, showing similar to uncertain effects in short term benefits and harms.

In people at higher risk of fractures (than used in the calculations of the baseline and absolute effects), the absolute

	a. post menopausal women with osteopaenia or osteoporosis (T score </= -1.6) - other subgroups available with T score >/= -2.5 b. Few events c. Cohort study analysis adjusted for age **Baseline risks at 10 years without medication** Hip fracture 30/1000 person years Vertebral fractures (all including radiologically confirmed was used) 150/1000 person years Non-vertebral fractures (all fractures – vertebral = 300 – 150) 150/1000 person years Vertebral fractures, clinically diagnosed (high risk patient) 50 per 1,000 person-yrs All fractures 300 per 1000 **Risks with shorter duration bisphosphonates (Baseline risk over 5 years X RR with bisphosphonates from 3-5 year studies + baseline risk over 5 years)** Hip fracture (RR 0.65) 25/1000 Vertebral fractures (all including radiologically confirmed was used) (RR 0.6) 120/1000 Non-vertebral fractures (all fractures) (RR 0.8) 135/1000 Vertebral fractures, clinically diagnosed (high risk patient) (RR 0.6) 40 per 1,000 All fractures ~200 fractures (RR 0.7) 255 per 1000 **RISEDRONATE** High losses of follow-up in long term studies. <u>Sorensen 2003</u> Extended a 3-year, placebo-controlled vertebral fracture (VERT-MN) study in osteoporotic women for 2 years. 265 women (placebo, 130; 5 mg risedronate, 135) entered the study and 220 completed. New vertebral fractures in years 4 and 5 RRR: 59% (19 to 79%). Decreases in markers of bone turnover observed in the first 3 years were maintained. Increases in spine and hip bone mineral density were maintained or increased. The mean increase from baseline in lumbar spine BMD over 5 years was 9.3%. <u>Ste-Marie LG 2004</u> 74 women completed the additional 2 years on treatment (placebo, 33; risedronate, 41) (extension VERT-NA) Differences at 5 years: Lumbar spine BMD increased significantly in the risedronate group (9.2%), whereas no significant change was seen in the placebo group (0.26%). During the 2-year study extension nonvertebral fractures occurred in 7 patients in placebo and 2 patients in risedronate groups. **References** Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, Pack S, Wenderoth D, Cooper C, Reginster JY. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003 Feb;32(2):120-6.	beneficial effects (fractures) would be larger, and they would likely not be at higher risk of harms.

Ste-Marie LG, Sod E, Johnson T, Chines A. Five years of treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004 Dec;75(6):469-76.

ETIDRONATE

A review conducted by Wells 2008 review included short and long term studies: 8 studies (3 were for 4 years). Similar reductions in vertebral and non-vertebral fractures were found before or after 3 years. There were very uncertain effects on hip fractures (very few events), and similar withdrawal events in short and longer term.

Reference

Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004523.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See table below	The Guideline Panel identified important differences in AFF would be 25 more per 100 000 person years; and we found greater than this - 39 to 131 more. They also identified 5 more ONJ per 100 000 person years as important. We found 25 per 100,000 if taking bisphosphonates, and higher risk if >5 years intake. The Guideline panel agreed that there may be moderate harms with longer term bisphosphonates.

Outcomes	With therapy of up to 3-5 years	With longer therapy	Difference	Relative effect (95% CI)	Certainty of the evidence
Subtrochanteric or femoral shaft fracture DX with rare x-ray review follow up: 10 years	5 per 1,000	7 per 1,000 (1 to 71)	**2 more per 1,000** (4 fewer to 66 more)	**HR 1.33** (0.12 to 14.67)	⨁◯◯◯ VERY LOW[b]
serious adverse events - Atypical femoral fracture follow up: 10 years	Incidence of AFF without bisphosphonates 0.3/100 000 person years. From 2 to 6 years, there are 14-16 AFF per 100,000 per year; and 6 to 10+ years, there are 39 to 108 AFF per 100,000 per year (Dell 2012). In addition, Black (2020) reported at <3 years: 6/100 000; 3-5 years: 25/100 000; 5 to 8 years: 60/100 000; and after 8 years: 131/100 000. There may be a higher risk in women, and people of Asian ethnicity (~6 times higher, Black 2020).				⨁⨁◯◯ LOW[c]
serious adverse events - osteoneocrosis of the jaw follow up: 10 years	No cases were identified in 5 year or 10 year groups in the RCT. A recent cohort (Eiken 2017) reported 25 (95% confidence interval 2.1 to 3.1) per 100,000 patient years for users of bisphosphonates, and a higher risk in >5 years intake.				⨁⨁◯◯ LOW[b]

a. post menopausal women with osteopaenia or osteoporosis (T score </= -1.6) - other subgroups available with T score >/= -2.5
b. Few events

	c. Cohort study analysis adjusted for age **References** Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012;27(12):2544-50. Black DM, Geiger EJ, Eastell R, Vittinghoff E, Li BH, Ryan DS, et al. Atypical Femur Fracture Risk versus Fragility Fracture Prevention with Bisphosphonates. N Engl J Med. 2020;383(8):743-53. Eiken PA, Prieto-Alhambra D, Eastell R, Abrahamsen B. Surgically treated osteonecrosis and osteomyelitis of the jaw and oral cavity in patients highly adherent to alendronate treatment: a nationwide user-only cohort study including over 60,000 alendronate users. Osteoporos Int. 2017;28(10):2921-8.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Evidence is from a systematic review by Barrionuevo 2019 (search date up to March 2014) of 26 studies (cross-sectional/surveys and qualitative research studies, including focus groups and interviews) with 15,348 women, with a mean age of 66 years. Questions were related to bisphosphonates, denosumab, teriparatide, calcitonin, and hormone replacement therapy. Evidence was graded using CERQUAL, as moderate certainty evidence. "Women facing the decision of taking medications for osteoporosis appear to value effectiveness and side effects equally and to prefer medications given less frequently. Injectable drugs appear to be acceptable as long as they are given less frequently." Across the studies, the preferences were not affected by age, previous drug exposure, or employment status.	The Guideline panel placed more value on the serious adverse effects such as AFF and ONJ, and agreed that patients (and clinicians) would also place more weight on the AFF due to the serious consequences.

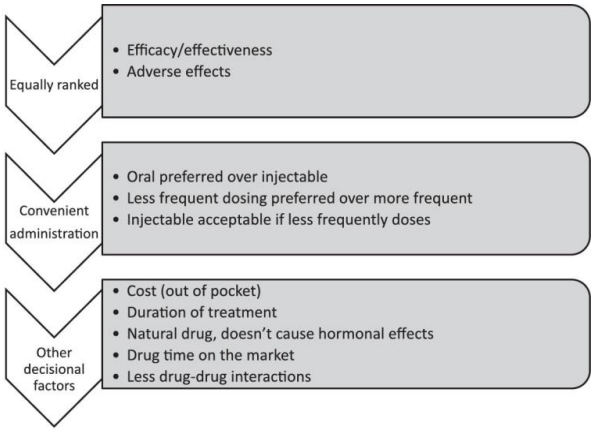


Figure 2. Summary of values and preferences relevant to osteoporosis treatments.

Reference

Barrionuevo P, Gionfriddo MR, Castaneda-Guarderas A, Zeballos-Palacios C, Bora P, Mohammed K, Benkhadra K, Sarigianni M, Murad MH. Women's Values and Preferences Regarding Osteoporosis Treatments: A Systematic Review. J Clin Endocrinol Metab. 2019 May 1;104(5):1631-1636.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	A patient survey conducted by Osteoporosis Canada of approximately 1000 members found that avoiding fractures and maintaining quality of life was important; as well as avoiding serious harms from medications. Evidence from a systematic review (Yeam 2018) of 124 articles. Prevalence of medication adherence ranged from 12.9 to 95.4%. Factors associated with poorer adherence: - polypharmacy - older age - misconceptions about osteoporosis, lack of patient education - higher dosing frequency - medication side effects - care under different medical specialties - current smoker - lack of medical insurance coverage References Morin SN, Djekic-Ivankovic M, Funnell L, Giangregorio L, Rodrigues IB, Ridout R, Feldman S, Kim S, McDonald-Blumer H, Kline G, Ward WE, Santesso N, Leslie WD. Patient engagement in clinical guidelines development: input from > 1000 members of the Canadian Osteoporosis Patient Network. Osteoporos Int. 2020 May;31(5):867-874. Yeam CT, Chia S, Tan HCC, Kwan YH, Fong W, Seng JJB. A systematic review of factors affecting medication adherence among patients with osteoporosis. Osteoporos Int. 2018 Dec;29(12):2623-2637.	The Guideline panel agreed that likely short term duration would be more acceptable because long-term adherence may be difficult and also due to media and fears of long-term adverse events. Therefore, most patients would be agreeable to stopping treatments after short-term therapy. Adherence and prescribing may be related to the fears of severe adverse events with long term use. The panel also agreed that patients may adhere better if they knew that treatment would be short term. The Guideline panel also agreed that costs would not be a barrier to duration of treatment (although some medicines may not be covered in some provinces). There are generic forms of the brand name oral bisphosphonates available which are lower cost. The costs would also be negligible if the medicines were provided long term.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes	No research evidence was found.	The guideline Panel agreed that longer term treatment is probably less feasible than

○ Varies ○ Don't know		shorter term due to the burden to patients and the health care system (e.g., monitoring). Follow-up is necessary as there is the risk that patients could stay on the medications for very long periods if switching providers or poor continuity of care. There may be different prescribing issues in some provinces, e.g., there are different allowances for different drugs (such as Etidronate and Alendronate in BC). Etidronate is still available and in use (e.g. as a second line therapy) but may be challenging to obtain in some provinces due to low supply.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals on bisphosphonates, we suggest initial therapy for a duration of 3 to 6 years.
Remarks: Six years of therapy is appropriate for individuals with a history of hip, vertebral, or multiple non-vertebral fractures, or new or ongoing risk factor(s) for accelerated bone loss or fracture. When using zoledronic acid, dosing less frequently than annually may be appropriate..
(GRADE: conditional- low certainty of evidence).

Three years after stopping bisphosphonate therapy (i.e. drug holiday), we suggest repeating BMD testing and clinical assessment of fracture risk to determine the need for resumption of therapy. We suggest following the recommendations for risk assessment and initiation of pharmacotherapy.
Remark: A shorter interval for reassessment to resume therapy may be appropriate in individuals with secondary causes of osteoporosis, new fracture or other active risk factors for rapid bone loss or fracture. (GRADE: conditional recommendation, very low certainty evidence).

When there is inadequate response or ongoing important concerns for fracture during bisphosphonate therapy, good practice includes extending or switching therapy, reassessing for secondary causes, and seeking advice from a consultant with expertise in osteoporosis if needed.
Remark: Inadequate response to treatment is considered when more than one fracture and/or substantial bone density decline (e.g., ≥ 5%) occurs despite adherence to an adequate course of treatment (typically >1 year). Fractures or bone density decline during therapy do not always indicate inadequate response to treatment (e.g. secondary causes of osteoporosis, falls, BMD imprecision errors). (Good practice statement).

Justification

Compared to shorter durations, taking oral bisphosphonates for ≥6 years likely results in no difference in hip or overall number of fractures, but a moderate to small reduction in clinically (22 fewer per 1000) and radiologically (17 fewer per 1000) identified vertebral fractures (3). Compared to 3 years, taking zoledronic acid for 6 years likely results in no difference in hip and non-vertebral fractures, but the effect is uncertain for radiologically confirmed vertebral fractures (11). Harms may be increased with longer durations of bisphosphonates: after 6 years there are 39-131 AFF and greater risk of ONJ after 5 years (12-14). At 6 years, these harms likely outweigh the benefits of therapy, except in people at higher risk of fractures.

DURATION OF IV ZOLEDRONIC ACID

QUESTION 3: SHOULD LONGER DURATION OF ZOLEDRONIC ACID VERSUS SHORTER DURATION BE RECOMMENDED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINED BY SUBGROUPS)?

QUESTION 5: SHOULD A CHANGE IN PHARMACOTHERAPY BE RECOMMENDED WHEN NEW FRACTURE(S) AND/OR UNEXPECTED BONE LOSS OCCURS WHILE ON EFFECTIVE TREATMENT VS. NO CHANGE IN PHARMACOTHERAPY, FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINE BY SUBGROUPS)?

Should longer duration versus shorter duration be used for individuals taking IV zoledronic acid?	
POPULATION:	individuals taking IV zoledronic acid
INTERVENTION:	longer duration of therapy
COMPARISON:	shorter duration
MAIN OUTCOMES:	hip fractures; non-vertebral fractures; vertebral fractures; harms (e.g., atypical femur fracture and osteonecrosis of the jaw)
SETTING:	Outpatient
PERSPECTIVE:	Population

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	We used a systematic review of randomised and non-randomised studies published by AHRQ in April 2019 (search up to October 2018). Studies included Black 2012 (6 years Zoledronic acid versus 3 years then 3 years placebo), Black 2015 (9 years zoledronic acid versus 6 years then 3 years placebo), Cosman 2014, McClung 2009, Reid 2018 (6 years). Reid 2018 provided zoledronic acid 5 mg at 18-month intervals IV for 6 years versus placebo 6 years; and measured outcomes annually. We also used the results from a network meta-analysis for the effects of IV zoledronic acid at 3 years: Barrionuevo 2019. Reference Fink HA, MacDonald R, Forte ML, Rosebush CE, Ensrud KE, Schousboe JT, Nelson VA, Ullman K, Butler M, Olson CM, Taylor BC, Brasure M, Wilt TJ. Long-Term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention: A Systematic Review. Comparative Effectiveness Review No. 218. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-00008-I) AHRQ Publication No. 19-EHC016-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2019. Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis. J Clin Endocrinol Metab. 2019;104(5):1623-30.	The effects of IV zoledronic acid provided annually for 3 years compared to placebo exceed the moderate benefits as determined by the panel. At 3 years the effects of 1 dose compared to annual doses were similar. The guideline panel agreed that the effects of IV zoledronic acid compared to placebo at 6 years versus 3 years: • For total factures a moderate reduction is 68 fewer, however we found 9 more with longer treatment; • For non-vertebral and hip fractures we found little to no difference. • For vertebral fractures (clinical only) 14 fewer is important and we found 32 more; however for radiologically confirmed we found 56 fewer and 41 fewer is important, a moderate reduction. The guideline panel agreed that at 6 years the effects of 4 doses for 6 years is likely similar to 6 annual doses and similar to 3 annual doses and then none, or 1 dose every 3 years.

Outcomes	With therapy up to 3 years	With longer therapy	Difference	Relative effect (95% CI)	Certainty of the evidence
hip fractures follow up: 3 years	10 per 1,000	**6 per 1,000** (5 to 8)	**4 fewer per 1,000** (6 fewer to 2 fewer)	**RR 0.60** (0.45 to 0.81)	⨁⨁⨁⨁ HIGH
non-vertebral fractures follow up: 3 years	50 per 1,000	**40 per 1,000** (34 to 47)	**10 fewer per 1,000** (16 fewer to 3 fewer)	**RR 0.79** (0.67 to 0.94)	⨁⨁⨁◯ MODERATE[a]
vertebral fractures follow up: 3 years	50 per 1,000	**19 per 1,000** (13 to 29)	**31 fewer per 1,000** (38 fewer to 21 fewer)	**RR 0.38** (0.25 to 0.58)	⨁⨁⨁◯ MODERATE[b]
any clinical fracture follow up: 6 years	264 per 1,000	**273 per 1,000** (196 to 376)	**9 more per 1,000** (68 fewer to 112 more)	**HR 1.04** (0.71 to 1.54)	⨁⨁⨁◯ MODERATE[b]

nonvertebral fractures follow up: 6 years	141 per 1,000	**140 per 1,000** (101 to 204)	**1 fewer per 1,000** (40 fewer to 63 more)	**HR 0.99** (0.70 to 1.50)	⊕⊕⊕◯ MODERATE[b]
hip fracture follow up: 6 years	26 per 1,000	**23 per 1,000** (9 to 63)	**3 fewer per 1,000** (17 fewer to 37 more)	**HR 0.90** (0.33 to 2.49)	⊕⊕◯◯ LOW[b]
Vertebral fractures assessed with: radiological follow up: 6 years	123 per 1,000	**67 per 1,000** (35 to 118)	**56 fewer per 1,000** (88 fewer to 5 fewer)	**OR 0.51** (0.26 to 0.95)	⊕⊕⊕⊕ HIGH
Vertebral fractures assessed with: clinical follow up: 6 years	41 per 1,000	**73 per 1,000** (22 to 229)	**32 more per 1,000** (19 fewer to 188 more)	**HR 1.81** (0.53 to 6.20)	⊕⊕⊕◯ MODERATE[a]
any clinical fractures (zolendronic acid up to 6 years then continue or placebo) follow up: 9 years	200 per 1,000	**219 per 1,000** (96 to 456)	**19 more per 1,000** (104 fewer to 256 more)	**HR 1.11** (0.45 to 2.73)	⊕⊕⊕◯ MODERATE[b]

a. Few events however confidence intervals do not include an important benefit.
b. Few events

Risks with zoledronic acid for short term (Baseline risk over 3 years X RR for Zoledronic acid from 3 year studies + baseline risk over 7 years)
Hip fracture (RR 0.6) 26/1000
Vertebral fractures (all including radiologically confirmed) (RR 0.4) 123/1000
Non-vertebral fractures (all fractures) (RR 0.8) 141/1000
Vertebral fractures, clinically diagnosed (high risk patient) (RR 0.4) 41 per 1,000
All fractures 264 fractures (0.6)

Long term effects at 6 years: IV zoledronic acid (4 doses every 18 months) versus placebo (Reid 2018)
Compared to placebo, IV zoledronic acid resulted in moderate benefits for incident clinical fractures, nonvertebral fractures, vertebral fractures, and hip fractures. The absolute effects were
•All fractures = 16.3% had a fracture after 6 years when taking zoledronic acid
•Nonvertebral = 10.1% had a fracture after 6 years when taking zoledronic acid
•Vert 1.4% had a fracture after 6 years when taking zoledronic acid

Effects at 3 years with annual dose or 1 dose (Reid 2013 – re-analysis of Horizon PFT and RFT)

	Horizon PFT: femoral neck BMD T-score of 2.5 or less with or without existing vertebral fracture or a femoral neck BMD T-score of 1.5 or less with at least 2 mild vertebral fractures or 1 moderate vertebral fracture (BLACK 2007) Horizon RFT: within 90 days of surgical repair of low trauma hip fracture (LYLES 2007) Effects on all clinical, clinical vertebral and nonvertebral were similar. Absolute incidence of nonvertebral fractures at 3 years was 6.7% after 1 dose. **References** Reid IR, Black DM, Eastell R, Bucci-Rechtweg C, Su G, Hue TF, Mesenbrink P, Lyles KW, Boonen S; HORIZON Pivotal Fracture Trial and HORIZON Recurrent Fracture Trial Steering Committees. Reduction in the risk of clinical fractures after a single dose of zoledronic Acid 5 milligrams. J Clin Endocrinol Metab. 2013 Feb;98(2):557-63. Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wong S, Wiessing KR, Bolland MJ, Bastin S, Gamble GD. Fracture Prevention with Zoledronate in Older Women with Osteopenia. N Engl J Med. 2018 Dec 20;379(25):2407-2416. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007 May 3;356(18):1809-22. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, Cummings SR, Hue TF, Lippuner K, Lakatos P, Leung PC, Man Z, Martinez RL, Tan M, Ruzycky ME, Su G, Eastell R. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012 Feb;27(2):243-54. doi: 10.1002/jbmr.1494. Erratum in: J Bone Miner Res. 2012 Dec;27(12):2612. Black DM, Reid IR, Cauley JA, Cosman F, Leung PC, Lakatos P, Lippuner K, Cummings SR, Hue TF, Mukhopadhyay A, Tan M, Aftring RP, Eastell R. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2015 May;30(5):934-44. Cosman F, Cauley JA, Eastell R, Boonen S, Palermo L, Reid IR, Cummings SR, Black DM. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? J Clin Endocrinol Metab. 2014 Dec;99(12):4546-54.	

	McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL. Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. Obstet Gynecol. 2009 Nov;114(5):999-1007. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007 Nov 1;357(18):1799-809.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Below are results from the randomised controlled trials reporting on serious adverse events from Fink 2019 (page D-35). We did not find any non-randomised studies reporting atypical femur fractures (AFF) or osteonecrosis of the jaw (ONJ) separately for IV zoledronic acid.	There were little data for ONJ and AFF in the randomised controlled trials, and no analyses from non-randomised studies specific to IV zoledronic acid. However, the Guideline Panel agreed that the increase in ONJ and AFF with long term oral bisphosphonates compared to shorter term, is likely greater when comparing long term to short term IV zoledronic, due to route of administration and greater anti-resorptive potency of IV zoledronic. The differences with long term oral bisphosphonates for AFF was 39 to 108 more per 100 000 person years (greater than an important increase of 25); and was greater than 25 per 100 000 person years for ONJ (which is greater than an

	Black 2012 (HORIZON extension) 6 yr Low	Mortality Zoledronic acid: 26/613 (4.2%) Placebo: 18/616 (2.9%) p=0.22 Myocardial infarction, any Zoledronic acid: 6/613 (1.0%) Placebo: 4/616 (0.6%) Myocardial infarction, severe Zoledronic acid: 5/13 (0.8%) Placebo: 4/616 (0.6%)	Afib, any Zoledronic acid: 21/613 (3.4%) Placebo: 13/616 (2.1%) p=0.17 Afib, severe Zoledronic acid: 12/613 (2.0%) Placebo: 7/616 (1.1%) p=0.26 AFF Zoledronic acid: 0/613 (0%) Placebo: 0/616 (0%) ONJ Zoledronic acid: 1/613 (<1%) Placebo: 0/616 (0%)	important increase of 5 more ONJ cases). This evidence was Low certainty for oral bisphosphonates.
	Black 2015 (HORIZON extension) 9 yr Low	Mortality Zoledronic acid: 1/92 (1.1%) Placebo: 5/95 (5.3%) p=0.21	Afib, any Zoledronic acid: 5/92 (5.4%) Placebo: 1/95 (1.1%) p=0.11 Afib, severe Zoledronic acid: 1/92 (1.1%) Placebo: 1/95 (1.1%) p=1.0 AFF Zoledronic acid: 0/92 (0%) Placebo: 0/95 (0%) ONJ Zoledronic acid: 0/92 (0%) Placebo: 0/95 (0%)	

Certainty of evidence

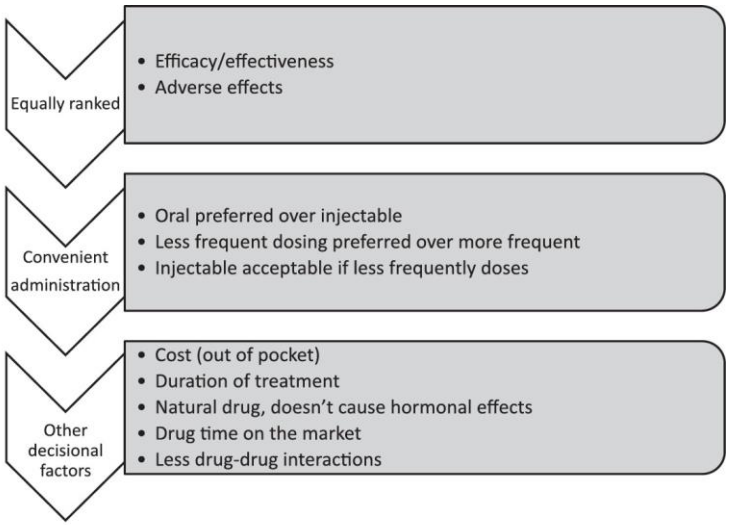
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		There is high certainty for the short term effects of IV zoledronic acid provided annually for 3 years. When comparing doses after 3 years or 6 years, there is low certainty evidence.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or	Evidence is from a systematic review by Barrionuevo 2019 (search date up to March 2014) of 26 studies (cross-sectional/surveys and qualitative research studies, including focus groups and	

variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	interviews) with 15,348 women, with a mean age of 66 years. Questions were related to bisphosphonates, denosumab, teriparatide, calcitonin, and hormone replacement therapy. Evidence was graded using CERQUAL, as moderate certainty evidence. "Women facing the decision of taking medications for osteoporosis appear to value effectiveness and side effects equally and to prefer medications given less frequently. Injectable drugs appear to be acceptable as long as they are given less frequently." Across the studies, preferences were not affected by age, previous drug exposure, or employment status.  **Figure 2.** Summary of values and preferences relevant to osteoporosis treatments. **Reference** Barrionuevo P, Gionfriddo MR, Castaneda-Guarderas A, Zeballos-Palacios C, Bora P, Mohammed K, Benkhadra K, Sarigianni M, Murad MH. Women's Values and Preferences Regarding Osteoporosis Treatments: A Systematic Review. J Clin Endocrinol Metab. 2019 May 1;104(5):1631-1636.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	Probably favours not providing long term IV zoledronic acid (the comparator) in people at high risk of fractures. However, for people at higher risk with a history of fractures, long term is probably favoured over short term.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		There are differences in drug coverage by province , however generic forms of iv zoledronic acid at lower costs are available. Although costs of stopping would be less expensive, the costs are not significant.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	A patient survey conducted by Osteoporosis Canada of approximately 1000 members found that avoiding fractures and maintaining quality of life was important; as well as avoiding serious harms from medications. Evidence from a systematic review (Yeam 2018) of 124 articles. Prevalence of medication adherence ranged from 12.9 to 95.4%. Factors associated with poorer adherence: - polypharmacy - older age - misconceptions about osteoporosis, lack of patient education - higher dosing frequency - medication side effects - care under different medical specialties - current smoker - lack of medical insurance coverage References	The Guideline panel agreed that likely short term duration would be more acceptable due to media and fears of adverse events. Therefore, most patients would likely be agreeable to stopping treatment after short-term therapy.

	Morin SN, Djekic-Ivankovic M, Funnell L, Giangregorio L, Rodrigues IB, Ridout R, Feldman S, Kim S, McDonald-Blumer H, Kline G, Ward WE, Santesso N, Leslie WD. Patient engagement in clinical guidelines development: input from > 1000 members of the Canadian Osteoporosis Patient Network. Osteoporos Int. 2020 May;31(5):867-874. Yeam CT, Chia S, Tan HCC, Kwan YH, Fong W, Seng JJB. A systematic review of factors affecting medication adherence among patients with osteoporosis. Osteoporos Int. 2018 Dec;29(12):2623-2637.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was found.	Follow-up monitoring is necessary after and before each infusion. Finding an infusion centre/clinic for iv zoledronic administration may pose challenges in many communities and provinces; in particular in primary care settings. Although finding an infusion centre would have been arranged with short term provision already; there may be additional burden with long term treatment.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

For individuals on bisphosphonates, we suggest initial therapy for a duration of 3 to 6 years.
Remarks: Six years of therapy is appropriate for individuals with a history of hip, vertebral, or multiple non-vertebral fractures, or new or ongoing risk factor(s) for accelerated bone loss or fracture. When using zoledronic acid, dosing less frequently than annually may be appropriate..
(GRADE: conditional- low certainty of evidence).

Justification

Compared to shorter durations, taking oral bisphosphonates for ≥6 years likely results in no difference in hip or overall number of fractures, but a moderate to small reduction in clinically (22 fewer per 1000) and radiologically (17 fewer per 1000) identified vertebral fractures (3). Compared to 3 years, taking zoledronic acid for 6 years likely results in no difference in hip and non-vertebral fractures, but the effect is uncertain for radiologically confirmed vertebral fractures (11). Harms may be increased with longer durations

of bisphosphonates: after 6 years there are 39-131 AFF and greater risk of ONJ after 5 years (12-14). At 6 years, these harms likely outweigh the benefits of therapy, except in people at higher risk of fractures.

DURATION OF DENOSUMAB

QUESTION 4: SHOULD LONGER DURATION OF DENOSUMAB VERSUS SHORTER DURATION BE RECOMMENDED FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINED BY SUBGROUPS)?

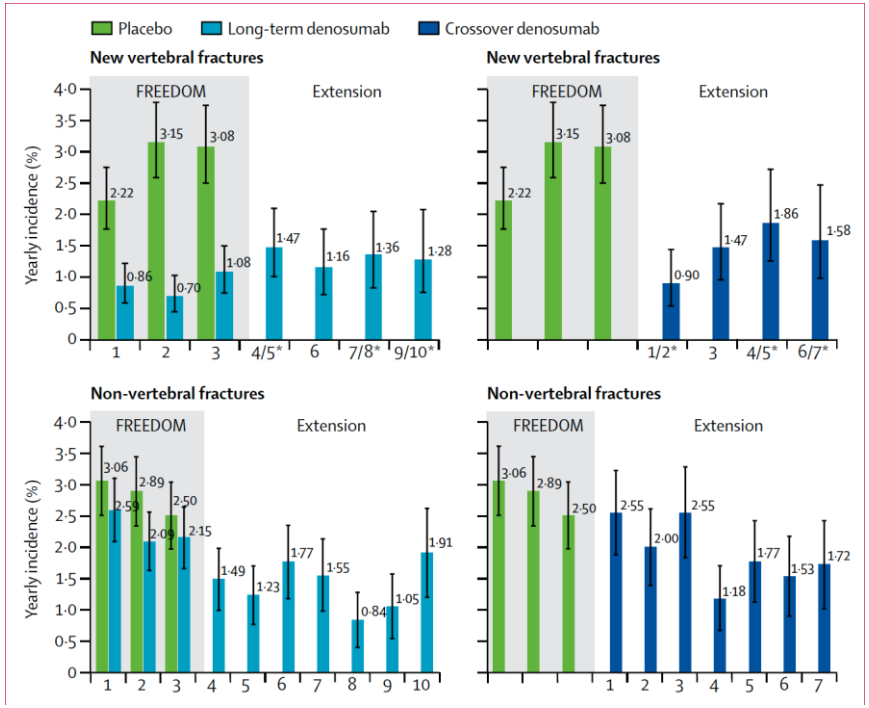
QUESTION 5: SHOULD A CHANGE IN PHARMACOTHERAPY BE RECOMMENDED WHEN NEW FRACTURE(S) AND/OR UNEXPECTED BONE LOSS OCCURS WHILE ON EFFECTIVE TREATMENT VERSUS NO CHANGE IN PHARMACOTHERAPY, FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINE BY SUBGROUPS)?

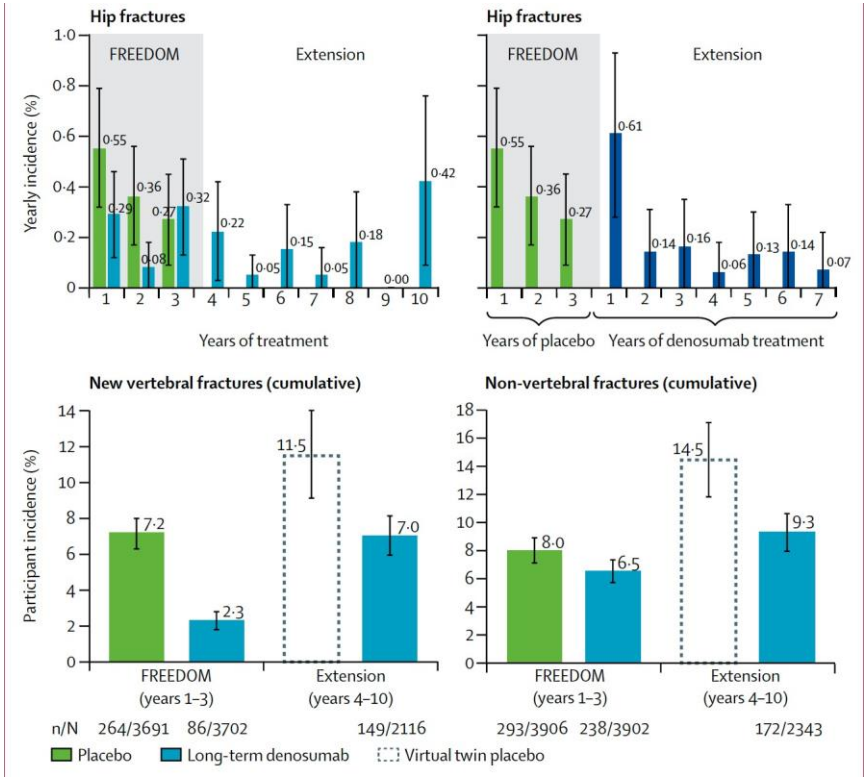
Should longer duration versus shorter be used for individuals taking denosumab?	
POPULATION:	individuals taking denosumab
INTERVENTION:	Longer duration of therapy
COMPARISON:	Shorter duration
MAIN OUTCOMES:	Fractures; AFF or ONJ; Serious adverse events
SETTING:	Outpatient
PERSPECTIVE:	Population

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	We used data from a systematic review published by AHRQ (Fink 2019) and data from Bone 2017. **FRACTURES with treatment over 10 years** (graphs from Bone 2017)	The evidence suggests that reductions in vertebral fractures are maintained after 3 years up to 10 years of treatment, and the reductions in non-vertebral fractures may be greater after 3 years. The guideline group agreed that there may be moderate benefits beyond 3 years.


Placebo
Long-term denosumab
Crossover denosumab
New vertebral fractures
FREEDOM
Extension
Yearly incidence (%)
2·22
3·15
3·08
0·86
0·70
1·08
1·47
1·16
1·36
1·28
1
2
3
4/5*
6
7/8*
9/10*
New vertebral fractures
FREEDOM
Extension
2·22
3·15
3·08
0·90
1·47
1·86
1·58
1/2*
3
4/5*
6/7*
Non-vertebral fractures
FREEDOM
Extension
Yearly incidence (%)
3·06
2·59
2·89
2·09
2·50
2·15
1·49
1·23
1·77
1·55
0·84
1·05
1·91
1
2
3
4
5
6
7
8
9
10
Non-vertebral fractures
FREEDOM
Extension
3·06
2·89
2·50
2·55
2·00
2·55
1·18
1·77
1·53
1·72
1
2
3
4
5
6
7



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Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, Czerwiński E, Fahrleitner-Pammer A, Kendler DL, Lippuner K, Reginster JY, Roux C, Malouf J, Bradley MN, Daizadeh NS, Wang A, Dakin P, Pannacciulli N, Dempster DW, Papapoulos S. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017 Jul;5(7):513-523.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**SERIOUS ADVERSE EVENTS** (Table from Bone 2017)	Overall, there appear to be higher rates of ONJ (although may be under-reporting with bisphosphonates), but fewer AFF compared bisphosphonates. Serious adverse events: suggested that there may be no increases over time (e.g., malignancies, infection, fatal adverse events, hypocalcaemia, eczema). Risks do not appear to increase with longer duration of the treatment.

	Placebo			Combined denosumab groups									
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Number of participants	3883	3687	3454	6085	5787	5452	4099	3890	3582	3261	1743	1585	1451
All adverse events	189·5	156·3	132·8	165·3	137·8	124·6	129·9	110·9	110·0	108·4	107·6	109·5	95·9
Infections	38·6	33·9	31·7	35·1	30·3	29·5	29·1	26·0	27·2	26·5	27·0	27·0	23·0
Malignancies	1·8	1·6	1·5	1·9	1·5	2·2	2·3	2·4	2·2	2·7	1·7	2·6	1·6
Eczema	0·8	0·5	0·6	1·4	1·1	1·0	1·1	1·2	0·9	0·7	0·8	0·9	1·3
Hypocalcaemia	<0·1	0	<0·1	<0·1	<0·1	0	<0·1	0·1	0	<0·1	<0·1	0	0·1
Pancreatitis	<0·1	<0·1	0	<0·1	<0·1	<0·1	0	<0·1	0·1	<0·1	0·1	<0·1	0
Serious adverse events	11·7	11·9	10·8	12·0	11·5	12·3	11·5	12·9	12·6	14·4	11·5	13·1	12·3
Infections	1·1	1·4	1·4	1·5	1·6	1·4	1·4	1·3	1·9	2·3	1·2	1·5	2·6
Cellulitis or erysipelas	0	0	<0·1	<0·1	<0·1	0·2	<0·1	<0·1	0·1	<0·1	0·2	<0·1	0·1
Fatal adverse events	0·8	0·8	1·0	0·7	0·6	0·7	0·5	0·8	0·9	1·5	0·7	1·0	0·9
Osteonecrosis of the jaw	0	0	0	0	<0·1	0	<0·1	0	0·2	<0·1	0	<0·1	<0·1
Atypical femoral fracture	0	0	0	0	0	<0·1	0	0	0	<0·1	0	0	0

Analyses were based on the original randomised treatment groups in FREEDOM. Data include all participants who received at least one dose of investigational product in FREEDOM or the extension. Placebo data are for all participants who received at least one dose of placebo during FREEDOM. Denosumab data are for all participants who received at least one dose of denosumab during FREEDOM or the extension. Data are shown for each year of exposure; thus a long-term participant could have up to 10 years of exposure and a crossover participant could have up to 7 years of exposure to denosumab. All adverse and serious adverse events were coded using Medical Dictionary for Regulatory Activities version 13.0.

Table 2: **Yearly exposure-adjusted participant incidence of adverse events per 100 participant-years of follow-up for placebo and for the combined FREEDOM, long-term, and crossover denosumab participants, up to 10 years**

AFF: 8 per 100 000 with 7 to 10 years denosumab (adjudicated). Risk with bisphosphonates at 6-10 years is 40-100/100 000 - denosumab is lower than bisphosphonates

ONJ: after 7 to 10 years of denosumab there was 52 per 100 000 patient years. Risk with bisphosphonates > 5 years is 25/100 000. Risk is higher with denosumab (although may be under-reporting with bisphosphonates from observational data and RCT data because may not have been recorded in the older studies).

Systematic review of INFECTIONS UP TO 4 YEARS

Systematic review (Diker-Cohen 2020) included 33 RCTs published from 2008-2019 with 22 253 patients followed up to 38 months, but typically 12-24 months (18 studies in primary osteoporosis).

	Absolute risk of serious infection was 1%; compared to placebo RR 1.23; compared to bisphosphonates RR 1.07; compared to teriparatide RR 1.55. Risk greater with duration more than 12 months RR 1.24 (1.05-1.46) compared to RR 1.06 (0.72-1.57) Reference Diker-Cohen T, Rosenberg D, Avni T, Shepshelovich D, Tsvetov G, Gafter-Gvili A. Risk for Infections During Treatment With Denosumab for Osteoporosis: A Systematic Review and Meta-analysis. J Clin Endocrinol Metab. 2020 May 1;105(5):dgz322.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Probably favours longer duration of therapy	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Denosumab is ~$800 per year which is relatively higher than bisphosphonates. Denosumab costs approximately 2-3 times higher than bisphosphonates.	The guideline panel agreed that some people will not meet criteria for funding or have coverage and therefore could be moderate costs. For hIgh risk people the costs of denosumab could be covered similar to other osteoporotic medications. The guideline group agreed that denosumab may not be cost-effective to provide over long durations in people who do not have a history of fracture.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	From a systematic review (Ban 2019) Persistence with denosumab therapy declines over time in adults ≥66 years: 74.8% persisted ≥ 1 year, 59.0% persisted ≥ 2 years, 48.1% persisted for ≥ 3 years, and 37.7% persisted ≥ 4 years.	Although persistence with therapy may decline, the guideline panel agreed that longer therapy is probably acceptable to people.

	Reference Ban JK, Hao BB, McCarthy L, Guilcher SJT, Cadarette SM. Denosumab utilization among older adults in Ontario: patient characteristics, persistence with therapy, and return to therapy after an extended gap. Osteoporos Int. 2019;30(9):1865-72.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Injections are relatively easy to receive from general practitioner, or by self-injection. There may be some challenges ensuring that they receive the injections on time. However, timing is feasble. Access may be more limited in some provinces.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

5.1 ***For individuals on denosumab, we suggest long term uninterrupted therapy*** [GRADE: conditional recommendation, low certainty evidence].
Remarks: The injection schedule of every 6 months should not be delayed by more than 1-2 months due to the risk of rapid bone loss and vertebral fractures. Duration of therapy may be assessed after 6-10 years and may be dependent on prior bisphosphonate therapy and individualized risk for atypical femoral fracture and osteonecrosis of the jaw.

Justification

Overall, the evidence suggests there are moderate benefits of longer therapy that are maintained or increase over time (up to 10 years). There are also small harms, including a low risk of atypical femur fractures, osteonecrosis of the jaw and other serious adverse events. The costs may be moderate, but injections are likely acceptable and feasible.

POST DENOSUMAB, TERIPARATIDE, ROMOSOZUMAB

QUESTION 6: SHOULD AN ALTERNATIVE MEDICATION BE RECOMMENDED AFTER TAKING DENOSUMAB FOR A SPECIFIED DURATION TO PREVENT RAPID BONE LOSS AND RISK OF REBOUND VERTEBRAL FRACTURES, FOR POSTMENOPAUSAL FEMALES AND MALES AFED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES (DEFINED BY SUBGROUPS)?

QUESTION 7: SHOULD ANTI-RESORPTIVE THERAPY BE RECOMMENDED AFTER TAKING ANABOLIC THERAPY (TERIPARATIDE OR ROMOSOZUMAB) TO PREVENT LOSS OF BONE DENSITY GAINS FOR POSTMENOPAUSAL FEMALES AND MALES AGED 50 YEARS AND OLDER, WHO ARE AT RISK OF OSTEOPOROTIC FRACTURES?

Should an alternative medication versus none be used for individuals after taking denosumab (for <2 years), teriparatide or romozosumab?	
POPULATION:	individuals taking denosumab (for <2 years), teriparatide or romozosumab
INTERVENTION:	Alternative medication
COMPARISON:	none
MAIN OUTCOMES:	fractures (surrogate BMD); adverse events
SETTING:	outpatient
PERSPECTIVE:	population

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**DENOSUMAB** A systematic review of the literature narratively summarised the results from few and small comparative studies and case series that provide data about stopping denosumab with most after an average of 2-3 years of treatment [Tsourdi 2020 and references below to included studies)].	

	There is low certainty evidence from these studies that stopping denosumab may result in a decline in bone density to levels at or below levels when starting denosumab, and may increase the risk of vertebral fractures (including multiple vertebral fractures). The magnitude of the risk in specific populations is currently uncertain, although evidence suggests longer duration of treatment (e.g., greater than 2.5 years) or history of or prevalent vertebral fractures may increase risk. Few randomised and non-randomised studies assess the effects of providing bisphosphonates after stopping denosumab and follow patients up to 1-3 years. The effects of zoledronic acid or oral bisphosphonates may reduce bone loss similarly, however, the duration of follow-up treatment was not consistent across studies. References Tsourdi E, Zillikens MC, Meier C, Body JJ, Gonzalez Rodriguez E, Anastasilakis AD, Abrahamsen B, McCloskey E, Hofbauer LC, Guañabens N, Obermayer-Pietsch B, Ralston SH, Eastell R, Pepe J, Palermo A, Langdahl B. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. J Clin Endocrinol Metab. 2020 Oct 26:dgaa756. Everts-Graber J, Reichenbach S, Ziswiler HR, Studer U, Lehmann T. A Single Infusion of Zoledronate in Postmenopausal Women Following Denosumab Discontinuation Results in Partial Conservation of Bone Mass Gains. J Bone Miner Res. 2020 Jul;35(7):1207-1215. Anastasilakis AD, Papapoulos SE, Polyzos SA, Appelman-Dijkstra NM, Makras P. Zoledronate for the Prevention of Bone Loss in Women Discontinuing Denosumab Treatment. A Prospective 2-Year Clinical Trial. J Bone Miner Res. 2019 Dec;34(12):2220-2228. doi: 10.1002/jbmr.3853. Epub 2019 Oct 14. PMID: 31433518. Sølling AS, Harsløf T, Langdahl B. Treatment with Zoledronate Subsequent to Denosumab in Osteoporosis: a Randomized Trial. J Bone Miner Res. 2020 Oct;35(10):1858-1870. Eastell R, Christiansen C, Grauer A, Kutilek S, Libanati C, McClung MR, Reid IR, Resch H, Siris E, Uebelhart D, Wang A, Weryha G, Cummings SR. Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. J Bone Miner Res. 2011 Mar;26(3):530-7. Leder BZ, Tsai JN, Jiang LA, Lee H. Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: The Denosumab and Teriparatide Follow-up study (DATA-Follow-up). Bone. 2017;98:54-8. Ebina K, Hashimoto J, Kashii M, et al. Effects of follow-on therapy after denosumab discontinuation in patients with postmenopausal osteoporosis [published online ahead of print, 2020 Jun 8]. Mod Rheumatol. 2020;1-8. doi:10.1080/14397595.2020.1769895	

	Kendler D, Chines A, Clark P, Ebeling PR, McClung M, Rhee Y, Huang S, Stad RK. Bone Mineral Density After Transitioning From Denosumab to Alendronate. J Clin Endocrinol Metab. 2020 Mar 1;105(3):e255–64. **ANABOLIC THERAPY (TERIPARATIDE AND ROMOZOSUMAB)** Few and small studies have found that stopping anabolic treatment without follow-up anti-resorptive therapy may risk the loss of bone density gains, however providing an anti-resorptive agent such as alendronate or denosumab may prevent bone loss: - McClung 2018 found that BMD continued to increase when romosozumab was followed by denosumab, but returned to pre-treatment BMD with placebo (McClung et al., 2018); and - Saag 2017 also found reductions in fractures with 1 year of romosozumab followed by 1 year alendronate compared to alendronate for 2 years (Saag et al., 2017). - Leder 2009 found that BMD declined within 1 year after discontinuing teriparatide, but not to pre-treatment levels (Leder et al., 2009), and in another study that treatment with antiresorptives after discontinuation may reduce the loss of BMD (Leder, Tsai, Jiang, & Lee, 2017). References McClung, M. R., Brown, J. P., Diez-Perez, A., Resch, H., Caminis, J., Meisner, P., . . . Grauer, A. (2018). Effects of 24 Months of Treatment With Romosozumab Followed by 12 Months of Denosumab or Placebo in Postmenopausal Women With Low Bone Mineral Density: A Randomized, Double-Blind, Phase 2, Parallel Group Study. J Bone Miner Res, 33(8), 1397-1406. Saag, K. G., Petersen, J., Brandi, M. L., Karaplis, A. C., Lorentzon, M., Thomas, T., . . . Grauer, A. (2017). Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N Engl J Med, 377(15), 1417-1427. Leder, B. Z., Neer, R. M., Wyland, J. J., Lee, H. W., Burnett-Bowie, S. M., & Finkelstein, J. S. (2009). Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. J Clin Endocrinol Metab, 94(8), 2915-2921. doi:10.1210/jc.2008-2630 Leder, B. Z., Tsai, J. N., Jiang, L. A., & Lee, H. (2017). Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: The Denosumab and Teriparatide Follow-up study (DATA-Follow-up). Bone, 98, 54-58. doi:10.1016/j.bone.2017.03.006	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See above and Evidence to Decision tables for Individuals initiating therapy: anti-resorptive therapy had trivial harms.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or ariability	See Evidence to Decision tables for Individuals initiating therapy.	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor intervention or comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	See Evidence to Decision tables for Individuals initiating therapy.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	See Evidence to Decision tables for Individuals initiating therapy.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	See Evidence to Decision tables for Individuals initiating therapy.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For individuals discontinuing denosumab after 4 or fewer doses, we suggest transitioning to a bisphosphonate 6-8 months after the last dose of denosumab to reduce the risk of rapid bone loss. We suggest bisphosphonate therapy for 1 year and then reassessing the need for ongoing transition therapy.

Remark:

Discontinuation of denosumab may be appropriate for individuals for whom denosumab is no longer warranted, or for those who develop intolerance or contraindications to denosumab.

For individuals discontinuing denosumab after more than 5 or more doses, where the risk of rapid bone loss or vertebral fractures is high (e.g., those with prevalent vertebral fractures), good practice includes seeking advice from a consultant with expertise in osteoporosis on how to transition to an alternative therapy. (Good practice statement).

After a course of anabolic therapy, we suggest transitioning to an antiresorptive agent to maintain bone density gains
(GRADE: conditional- low certainty of evidence).

Justification

Overall, there may be moderate benefits and trivial harms providing anti-resorptive therapy after taking denosumab (for <2 years), or teriparatide or romozosumab. The costs of anti-resorptive therapy is negligible, they are also feasible and acceptable to take and provide.