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Systematic Review

CADTH

Denosumab, Raloxifene, and Zoledronic Acid for the Treatment of Postmenopausal Osteoporosis: Clinical Effectiveness and Harms

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Supporting Informed Decisions

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Canadian Agency for Drugs and Technologies in Health

Denosumab, Raloxifene, and Zoledronic Acid for the Treatment of Postmenopausal Osteoporosis: Clinical Effectiveness and Harms

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Health technology assessment agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision-making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Rapid Response Service provides Canadian health care decision-makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by Rapid Response Service is tailored to meet the needs of decision-makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this Rapid Response assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

This report is a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") that are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of reviewers.

ACRONYMS AND ABBREVIATIONS

AE	adverse event
BMD	bone mineral density
CI	confidence interval
DB RCT	double-blind randomized controlled trial
HR	hazard ratio
IV	intravenous
ONJ	osteonecrosis of the jaw
RANKL	receptor activator of nuclear factor-κB ligand
RCT	randomized controlled trial
RR	relative risk

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EXECUTIVE SUMMARY

Context and Policy Issues

Osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing patients to an increased risk of fracture. The postmenopausal form of osteoporosis affects more than 1.5 million Canadians, with prevalence increasing from 6% of women aged 50 to 59 years to more than 40% of women aged 80 years and older.[1] Consequences of sustaining a fracture may be serious and include increased risk of subsequent fractures, hospitalization or institutionalization, decreased quality of life, and premature mortality, with a related burden on the health care system.[2] Antiresorptive agents such as oral bisphosphonates are the standard treatment for postmenopausal osteoporosis, in conjunction with non-pharmacologic measures.[3] Other treatment options include an intravenous bisphosphonate (zoledronic acid), a monoclonal antibody (denosumab), a bone-forming agent (teriparatide), and a selective estrogen receptor modulator (raloxifene). This systematic review was undertaken following a request from provincial drug formularies to evaluate the clinical effectiveness and harms of three of these agents, denosumab, raloxifene, and zoledronic acid, in postmenopausal women with osteoporosis. The evidence gathered is expected to clarify uncertainty regarding these agents and to inform policy-making in the population of interest.

Research Question

What are the benefits and harms (based on pre-specified patient outcomes) of denosumab, raloxifene, and zoledronic acid in postmenopausal women with osteoporosis?

Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, EMBASE, The Cochrane Library, and PubMed. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs). Where possible, retrieval was limited to the human population. The search was also limited to the English language. Regular alerts were established to update the search until October 28, 2011. Conference abstracts were excluded from the search results. Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/grey-matters). Google and other internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Two reviewers independently screened citations and selected articles based on the inclusion criteria. The reviewers independently extracted the clinical effectiveness and harms outcome data and critically appraised the selected studies.

Summary of Findings

We identified six RCTs, whose results were reported in 20 published articles assessing the efficacy and safety of denosumab (one RCT), zoledronic acid (one RCT), or raloxifene (four RCTs) in the treatment of postmenopausal women with osteoporosis. No active-controlled RCTs were identified in the literature search; only placebo-controlled RCTs were retrieved. Therefore, no direct treatment comparisons were available to assess the relative efficacy of the drugs. We considered, but elected not to perform, indirect comparisons between the trials, considering substantial heterogeneity in patient populations and significant challenges limiting the use of statistical adjustments to manage heterogeneity, which were beyond the scope of this report.

Efficacy

The current evidence revealed that denosumab, zoledronic acid, and raloxifene were all effective in reducing the risk of vertebral fractures, both clinically and radiographically assessed (morphometric), after 36 months of treatment compared with placebo. Denosumab and zoledronic acid reduced the risk of multiple vertebral fractures, hip fractures, and non-vertebral fractures. The included trials only provided limited evidence regarding the effect of raloxifene at the recommended dosage of 60 mg daily on these outcomes, which suggested that it may not be effective in preventing non-vertebral fractures, including hip fractures. Such a conclusion is consistent with other literature indicating that raloxifene has not been shown to reduce non-vertebral fractures.[4]

Denosumab, zoledronic acid, and raloxifene were each associated with an increase in bone mineral density (BMD) compared with placebo after 36 months of treatment and up to seven years in one trial for raloxifene.[5] Nevertheless, the clinical relevance of these findings remains uncertain. Although T-scores are commonly used in clinical practice for monitoring purposes, change in BMD does not always correlate with change in fracture risk, which is a complex multifactorial issue. Therefore, clinical patient outcomes such as fractures are preferred to assess the efficacy of osteoporosis agents. The evidence for health-related quality of life and hospitalizations/long-term care needs was not sufficient to assess the effect of denosumab, zoledronic acid, or raloxifene on these outcomes.

Harms

The proportion of patients who died during the trials, as well as the overall incidence of serious adverse events, was not significantly different between each active drug and placebo. Nevertheless, some specific toxicities were reported more frequently with denosumab, zoledronic acid, and raloxifene. In the included trials, denosumab was associated with a higher incidence of cellulitis, zoledronic acid with atrial fibrillation, and raloxifene with venous thromboembolism and hot flushes compared with placebo. While thromboembolic events have been established as a major concern with the use of raloxifene,[4,6] additional data regarding atrial fibrillation with zoledronic acid suggest that they may have been false signals.[7,8]

The incidence of osteonecrosis of the jaw and atypical fractures was low and not significantly different between the active drugs and placebo in the trials. These are uncommon adverse events and, as a result, the findings from the included trials should not exclude a potential relationship with the active drugs. Despite no evidence of renal toxicity in HORIZON-PFT, zoledronic acid has been associated with renal dysfunction and therefore should not be used in patients with severe renal impairment and be used with caution in the presence of other products that could impact renal function.[7]

Conclusions and Implications for Decision- or Policy-Making

Six placebo-controlled RCTs were included in this systematic review, assessing the efficacy and safety of denosumab, zoledronic acid, and raloxifene in the treatment of postmenopausal women with osteoporosis. No direct comparison between these drugs was identified. Denosumab and zoledronic acid both reduced the risk of vertebral, hip, and non-vertebral fractures. While raloxifene was associated with a reduced incidence of vertebral fractures, the included trials only provided limited evidence regarding hip and non-vertebral fractures, although these fractures have clinically important consequences. The results suggest that raloxifene may not be effective in preventing hip and non-vertebral fractures, which is consistent with other reports.[4] We considered, but elected not to perform, indirect comparisons between the trials: significant challenges limited the use of statistical adjustments to manage heterogeneity, which were beyond the scope of this report. Therefore, the characteristics of each trial population should be considered when making a treatment decision. All three drugs were associated with a relative increase in BMD compared with placebo, but the clinical relevance of this is uncertain because changes in BMD do not always correlate with changes in fracture risk.

Mortality data and the incidence of serious adverse events did not raise new safety concerns. Nevertheless, some specific toxicities were reported more frequently with denosumab, zoledronic acid, or raloxifene compared to placebo and therefore specific harms profiles should be considered in the selection of these agents.

No evidence was identified to evaluate the efficacy and harms of these drugs as a second-line treatment option for postmenopausal women with intolerance or inadequate response to oral bisphosphonates, although this population may be prescribed these medications.

1 CONTEXT AND POLICY ISSUES

1.1 Osteoporosis

Osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing patients to an increased risk of fracture. Consequences of sustaining a fracture may be serious and include increased risk of subsequent fractures, hospitalization/institutionalization, decreased quality of life, and premature mortality, with a related burden on the health care system.[2] The postmenopausal form of osteoporosis is particularly prevalent, as a decrease in estrogen concentrations with the onset of menopause leads to increased bone resorption, which can compromise bone strength and predispose a patient to fractures over time. Osteoporosis affects more than 1.5 million Canadians, with prevalence increasing from 6% of women aged 50 to 59 years to more than 40% of women aged 80 years and older.[1]

Factors contributing to bone strength include bone density and geometry, degree of mineralization, microarchitecture, and abnormalities in bone tissue turnover where bone resorption is in excess of bone formation.[9] Traditionally, osteoporosis has been diagnosed based solely on low bone mineral density (BMD), as measured by a T-score equal to or less than –2.5. However, well-established risk factors for osteoporotic fractures also include older age and history of fragility fracture, which is a strong predictor of future fractures.[1] Other risk factors include a parental history of hip fracture, current tobacco use, long-term use of oral glucocorticoids, and high alcohol consumption.[2] Since patients with the highest risk of fracture are the ones most likely to benefit from therapy,[10] guidelines from Osteoporosis Canada released in October 2010[11] propose a paradigm shift in the prevention and treatment of osteoporotic fractures. Rather than focusing on treating a patient with low BMD, the organization now recommends identifying patients at risk of fragility fracture.

1.2 Post-fracture osteoporosis care gap

Current data suggest that there is a therapeutic gap between fragility fracture occurrence and subsequent appropriate osteoporosis assessment and treatment.[1,11,12] Indeed, the management of patients presenting with a fracture may focus on the fracture itself, rather than recognizing that it may be due to osteoporosis.[13] As a result, patients at high risk for fracture may not be identified or treated.[12] In addition, about half of patients who start osteoporosis medication will discontinue within the first year.[1] The 2010 Canadian Osteoporosis Guidelines[11] aim to raise awareness and to address the care gap for high-risk patients.

1.3 Treatment options

Antiresorptive agents such as oral bisphosphonates are the standard treatment for postmenopausal osteoporosis, in conjunction with non-pharmacologic measures whenever possible. These include regular exercise, adequate diet, including calcium and vitamin D intake, and avoidance of smoking, excessive alcohol intake, and caffeine intake.[3] For patients at risk of falls, fall-prevention strategies should also be implemented.[11]

Other treatment options include zoledronic acid, denosumab, teriparatide, and raloxifene. Although data suggest that estrogen therapy is effective in postmenopausal women with established osteoporosis,[14] it is no longer a first-line approach due to its risk-benefit profile. Our systematic review was undertaken following a request from provincial drug formularies and will focus on the benefits and harms of three drugs, denosumab, raloxifene, and zoledronic acid, in postmenopausal osteoporosis. These drugs are often used as second-line treatment options for postmenopausal women with intolerance or following an inadequate response to oral bisphosphonates. The need for information on teriparatide from provincial jurisdictions appeared to be lower and therefore the drug was not included in the review.

Denosumab

This fully human monoclonal antibody inhibits osteoclast-mediated bone resorption by binding to and neutralizing the activity of human receptor activator of nuclear factor-κB ligand (RANKL). Denosumab is indicated for the treatment of postmenopausal women at high risk for osteoporotic fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture; or for patients who have inadequate response or are intolerant to other available osteoporosis therapy. It is administered as a 60 mg subcutaneous injection every six months.

Raloxifene

Raloxifene is a selective estrogen receptor modulator indicated for the prevention and treatment of osteoporosis in postmenopausal women. According to the product monograph, raloxifene has estrogen agonist effects on bone and lipid metabolism concomitant with an estrogen antagonist effect on uterine and breast tissue. Consequently, raloxifene acts like estrogen to decrease the osteoclast-mediated bone resorption and improve bone mineral density, hence decreasing the risk of fracture. The recommended dosing regimen is one tablet of 60 mg once daily.

Zoledronic acid

Zoledronic acid, an injectable bisphosphonate agent, is an inhibitor of osteoclast-mediated bone resorption. The drug is indicated for the treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral, and non-vertebral fractures. The recommended dosing regimen is a once-yearly intravenous infusion of 5 mg of zoledronic acid.

1.4 Objectives of the systematic review

To determine the clinical effectiveness and harms of denosumab, raloxifene, and zoledronic acid compared with each other or with placebo in postmenopausal women with osteoporosis.

2 RESEARCH QUESTION

What are the benefits and harms (based on pre-specified patient outcomes) of denosumab, raloxifene, and zoledronic acid in postmenopausal women with osteoporosis?

3 KEY MESSAGE

Evidence from six placebo-controlled RCTs revealed that denosumab and zoledronic acid reduced the risk of vertebral, hip, and non-vertebral fractures in postmenopausal women with osteoporosis. Raloxifene was associated with a reduced incidence of vertebral fractures, but evidence was limited regarding hip and non-vertebral fractures, suggesting that it may not be effective in preventing such outcomes. Harms data did not raise new safety concerns; however, specific harms profiles should be considered when selecting treatment.

4 METHODS

The review protocol was developed jointly by the two clinical reviewers and the internal review team in consultation with an external clinical expert.

4.1 Literature search

A peer-reviewed literature search was developed based on three previous CADTH reports.[2,15,16] The updated literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to May 2011) with In-Process records and daily updates via Ovid; Embase (1996 to 2011) via Ovid; The Cochrane Library (2011, Issue 5) via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were raloxifene, denosumab, zoledronic acid, and osteoporosis. The searches were conducted within the following time frames (as updates to previous

CADTH reports that were conducted at different times): raloxifene (2001 to 2011), denosumab (September 2010 to 2011), zoledronic acid (December 2007 to 2011).

Methodological filters were applied to limit retrieval to health-technology assessments, systematic reviews, meta-analyses, and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to the English language. Regular alerts were established to update the search until October 28, 2011. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies. Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/grey-matters). Google and other internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

4.2 Selection Criteria and Methods

Evidence was considered for inclusion in the review based on the criteria outlined in Table 1. RCTs included in previous CADTH reports[2,15,16] (formulary reviews and health technology assessments) were considered. From the updated literature search, additional RCTs were selected by two clinical reviewers. All articles considered potentially relevant by at least one reviewer were acquired from library sources. The clinical reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion.

We searched for trials that would compare denosumab, raloxifene, and zoledronic acid with each other or with placebo. We excluded comparisons with oral bisphosphonates as they were not an intervention of interest in the systematic review.

Table 1: Selection Criteria

Population	Postmenopausal women with osteoporosis representative of the Canadian population.
Interventions	Denosumab (Prolia), 60 mg SC every 6 months. Raloxifene (Evista), 60 mg orally once daily. Zoledronic acid (Aclasta), 5 mg intravenous infusion once-yearly.
Comparators	Denosumab, raloxifene, or zoledronic acid at the appropriate dosage. Placebo.
Outcomes	Efficacy: • Vertebral, hip, and other non-vertebral fractures. • Quality of life, including pain, functional status, and independence. • Hospitalizations and institutionalizations (long-term care). • Change in BMD. Harms: Mortality, AEs, SAEs, WDs, and WDAEs.
Study Designs	DB RCTs identified in HTA reports and other reviews conducted by CADTH on the drugs and new relevant DB RCTs published since these CADTH reports.

AE = adverse event; DB RCT = double-blind randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WD = withdrawal; WDAE = withdrawal due to adverse events.

4.3 Exclusion criteria

Studies were excluded if they did not meet the selection criteria; presented preliminary results in an abstract form; or were duplicate publications, narrative reviews, or editorials.

4.4 Data extraction strategy

The review included published studies only. Two clinical reviewers proceeded with data extraction and the data were entered directly into evidence tables. The extracted data were verified for quality. Disagreements were resolved through discussion.

4.5 Critical appraisal of individual studies

Findings were interpreted in light of the heterogeneity of the individual studies (differences in design, study populations, interventions or exposures, and outcome measures) and the validity assessment. The SIGN 50 checklist[17] was used as a guide. Further critical appraisal was performed based on clinical input from experts.

4.6 Data analysis methods

Evidence tables describing the characteristics of the relevant studies were developed. We elected not to perform indirect comparisons between the trials, considering the substantial heterogeneity in patient populations. Significant challenges limited the use of statistical adjustments to manage heterogeneity, which were beyond the scope of this report. The low number of studies retrieved may have limited the validity of these adjustments. Therefore, the results of clinical effectiveness and harms are described using a narrative approach.

5 RESULTS

5.1 Quantity of Research Available

The literature search identified 1,137 articles, from which 108 were selected for full-text screening. A total of 20 articles reporting the results of six individual RCTs were included. The flow chart of selected articles is shown in Appendix 2. We searched for trials comparing denosumab, raloxifene and zoledronic acid with each other or with placebo. However, no active-controlled RCTs were identified in the literature search; only placebo-controlled RCTs were retrieved. No direct treatment comparisons were available.

5.2 Study Characteristics

A total of six published double-blind RCTs met the inclusion criteria: one for denosumab,[18] one for zoledronic acid,[19] and four for raloxifene .[5,20-22] FREEDOM (denosumab, n = 7,808), HORIZON PFT (zoledronic acid, n = 7,765), MORE (raloxifene, n = 7,705), and Silverman (raloxifene, n = 7,492) were manufacturer-sponsored trials of 36 months' duration assessing the impact of the drugs on fractures. The CORE BMD sub-study (raloxifene, n = 386) was the continuation from MORE. It included only a subset of the population based on specific criteria and assessed change in BMD after seven years of treatment with raloxifene. Michalska (raloxifene, n = 99) evaluated change in BMD over a shorter duration of 12 months. The trial required previous bisphosphonate treatment (> three years under alendronate) that would be stopped immediately prior to enrolment. The publication did not specify whether patients experienced inadequate response or intolerance to alendronate. All trials compared the respective interventions with placebo and provided calcium and vitamin D supplementation. The summary of study characteristics is shown in Appendix 3 and relevant patient baseline characteristics in Appendix 4.

A high-risk population is expected to benefit the most from osteoporosis treatment, which may bias the results in favour of the active drug and make it easier to show a fracture reduction.[10] As a result, the most relevant baseline characteristics are related to well-established risk factors for fragility fractures, such as older age, lower BMD, and history of fragility fractures.[1]There was heterogeneity in the patient populations across the trials with regard to these characteristics. Patients in the HORIZON PFT

and in the FREEDOM trials were older by six to eight years compared with those in the raloxifene trials. Inclusion criteria required a T-score < -2.5 at lumbar spine, total hip, or femoral neck; or low BMD and the presence of fractures. Baseline BMD measurements appeared slightly lower in FREEDOM and HORIZON PFT compared with the raloxifene trials. However, there was marked variation in the proportion of patients having a prevalent fracture at baseline. These proportions ranged from approximately 25% in FREEDOM and CORE, to 37% in MORE, 56% in Silverman, and almost 65% in HORIZON PFT. No information on baseline T-score or prevalent fracture status was available from the Michalska trial.

5.3 Critical Appraisal of Individual Studies

The studies were individually critically appraised and the details are available in Appendix 5. FREEDOM (denosumab) and the HORIZON PFT (zoledronic acid) were two large international, multicentre double-blind RCTs, including approximately 4,000 patients in each treatment arm. MORE and Silverman (raloxifene) were smaller, with approximately 2,500 and 1,800 patients, respectively, in each treatment arm. Only a subset of the MORE population was included in the CORE BMD sub-study, with a total of 386 patients in the trial (versus 7,705 patients in MORE for the three treatment arms). This is not considered effective to ensure between-group similarity. The Michalska trial was considerably smaller and had only 33 patients in each group.

Overall and despite some variation in the quality of the included trials, most of them showed an acceptable degree of methodological rigour. There were, however, some quality concerns, mainly related to insufficient reporting. This includes lack of information precluding a definite judgment on whether patients were adequately randomized to each treatment group and whether patients and investigators could foresee assignment to the treatment group. Information is also missing regarding maintenance of blindness of patients and investigators throughout the study duration. Likewise, patient withdrawals and reasons for discontinuation were often not reported.

Heterogeneity exists among the trial populations, especially with regard to the risk of fracture. A population with a higher risk of fracture is expected to experience a higher fracture rate when receiving a placebo, while the active drug is expected to markedly reduce the fracture rate, considering that a high-risk population is expected to benefit the most from osteoporosis treatment.[10] As a result, it is most likely easier for a drug to demonstrate benefits on fracture rates compared with placebo in a population at higher risk of fractures. Nevertheless, the trials were usually representative of the Canadian population of women living with osteoporosis. Patients who had recently used bisphosphonates before the start of the trial were, however, almost always excluded. Although this was appropriate for assessing the efficacy of the drugs, considering the residual effect of bisphosphonates on bone, the included patients may not be reflective of the general population, since oral bisphosphonates are widely used. No evidence was identified to evaluate the efficacy and harms of these drugs as a second-line treatment option for postmenopausal women with intolerance or inadequate response to oral bisphosphonates.

5.4 Data Analyses and Synthesis

5.4.1 Efficacy outcomes

A. Fractures

Fracture rates with zoledronic acid and denosumab are presented in Table 2, while the corresponding data for raloxifene are presented in Table 3. The CORE and Michalska trials did not assess fractures and therefore do not figure in the table or in the following section.

Table 2: Summary of Key Efficacy Outcomes for Zoledronic Acid and Denosumab at 36 Months										
	HORIZON PFT[19] (Zoledronic Acid)					FREEDOM[18] (Denosumab)				
	ZOL		PL		RR or HR (95%CI; P)	DEN		PL		RR or HR (95%CI; P)
	N	n* (%)	N	n* (%)		N	n* (%)	N	n* (%)	
New Vertebral Fractures	2,822	92 (3.3)	2,853	310 (10.9)	RR = 0.3 (0.24 - 0.38; P < 0.001)	3,702	86 (2.3)	3,691	264 (7.2)	RR = 0.32 (0.26 - 0.41; P < 0.001)
Multiple (> 2) New Vertebral	2,822	7 (0.2)	2,853	66 (2.3)	RR = 0.11 (0.05 - 0.23; P < 0.001)	3,702	23 (0.6)	3,691	59 (1.6)	RR = 0.39 (0.24 - 0.63; P < 0.001)
New Clinical† Vertebral	3,182	19 (0.5)	3,144	84 (2.6)	HR = 0.23 (0.14 - 0.37; P < 0.001)	3,902	29 (0.8)	3,906	92 (2.6)	HR = 0.31 (0.20 - 0.47; P < 0.001)
Hip Fractures	3,161	52 (1.4)	3,144	88 (2.5)	HR = 0.59 (0.42 - 0.83; P = 0.002)	3,902	26 (0.7)	3,906	43 (1.2)	HR = 0.6 (0.37-0.97; P = 0.04)
Non-vertebral Fractures‡	2,956	292 (8.0)	2,892	388 (10.7)	HR = 0.75 (0.64-0.87; P < 0.001)	3,902	238 (6.5)	3,906	293 (8.0)	HR = 0.8 (0.67 - 0.95; P = 0.01)

CI = confidence interval; DEN = denosumab; HR = hazard ratio; PL = placebo; RR = relative risk; ZOL = zoledronic acid.

*Number of patients with at least one fracture.

† Clinical vertebral fractures are symptomatic vertebral fractures that usually require medical intervention.

‡ The relative importance of non-vertebral fractures depends on whether they include hip fractures, which was impossible to identify from the publications.

Table 3: Summary of Key Efficacy Outcomes* for Raloxifene at 36 Months										
	MORE[20]					SILVERMAN[23]				
	RAL		PL		RR or HR (95% CI; P)	RAL		PL		RR or HR (95%CI; p)
	N	n† (%)	N	n† (%)		N	n† (%)	N	n† (%)	
New Vertebral Fractures	2,259	148 (6.6)	2,292	231 (10.1)	RR = 0.7 (0.5 to 0.8; P NR)	NR	NR	NR	NR	HR = 0.58 (0.38 to 0.89; P < 0.05)
New Clinical Vertebral	2,259	47 (2.1)	2,292	81 (3.5)	RR = 0.59 (0.41 to 0.83; P NR)	1,494 ‡	13 (0.9)	1,489 ‡	14 (0.9)	RR = 0.93§ (P not significant)
Hip Fractures¶	NR**	NR**	NR**	NR**	NR**	500	2 (0.4)	444	4 (0.9)	RR = 0.44 (P = 0.3)
Non-vertebral Fractures	NR**	NR**	NR**	NR**	NR**	1,508 ‡	89 (5.9)	1,571 ‡	99 (6.3)	RR = 0.94 (P = 0.6)
CI = confidence interval; HR = hazard ratio; NR = not reported; PL = placebo; RAL = raloxifene; RR = relative risk.										

* No data were found in the raloxifene trials pertaining to multiple vertebral fractures and therefore this outcome does not figure in the table.

† Number of patients with at least one fracture.

‡ The total number of patients in each treatment arm (N) was calculated by CADTH using the other data reported in the publication. They are however smaller than the corresponding numbers at baseline, 1,849 for raloxifene and 1,885 for placebo. No explanation was provided in the publication.

§ The relative risk was calculated by CADTH.

¶ Hip fractures in Silverman were assessed in a post-hoc analysis of a high-risk group. In each treatment arm, N was calculated by CADTH using the other data reported in the article.

** Data for hip and non-vertebral fractures were pooled for the two dosages of raloxifene in the MORE trial. Therefore, they were not extracted since they did not meet the inclusion criteria.

Vertebral fractures

Vertebral fractures are one of the most prevalent types of fragility fractures, affecting approximately one in four Canadian women 50 years of age and over.[2] This type of fracture can be either clinically- or radiographically identified (morphometric). More than two-thirds of new vertebral fractures belong to the second group. They are usually asymptomatic and do not come to clinical attention until multiple fractures occur.[2] There appears to be controversy in clinical practice regarding the importance of radiographically-identified fractures; nevertheless, they remain a frequent consequence of osteoporosis and a good predictor for subsequent fractures. Sustaining numerous vertebral fractures leads to clinically important outcomes, such as change in height and posture with ensuing obstructed breathing and abdominal capacities, increased risk of fall, chronic pain, and functional limitations accompanied by loss of independence.[1] Most trials reported radiographically-identified fractures as the primary outcome.

New vertebral fractures

After 36 months of treatment, there was a relative decrease of 68% in the incidence of vertebral fractures with denosumab compared with placebo (relative risk [RR] = 0.32, 95% CI, 0.26 to 0.41; P < 0.001) in the FREEDOM trial.[18] There was a relative decrease of 70% in HORIZON PFT with zoledronic acid compared with placebo in patients who were not taking any osteoporosis medications at the time of randomization (RR = 0.30, 95% CI, 0.24 to 0.38; P < 0.001). Statistical significance was reached in both trials. Detailed results are presented in Table 2.

Raloxifene resulted in a relative decrease of 30% in the incidence of vertebral fractures versus placebo in the MORE trial (RR = 0.70, 95% CI, 0.5 to 0.8; p value not reported).[20] Silverman[23] reported a HR = 0.58 (95% CI, 0.38 to 0.89; P < 0.05). In this trial, the absolute rate reduction in the incidence of new vertebral fractures for raloxifene compared with placebo at 36 months was 1.7% (data not shown; absolute fracture rates within each treatment arm were not reported).[23]

FREEDOM, HORIZON PFT, and MORE also reported intermediate results for new vertebral fractures after one year and after two years of treatment. The statistical comparison between the respective active treatments and placebo within each trial yielded statistically significant results (P < 0.001 for all comparisons).[18,19,24]

Multiple vertebral fractures

After 36 months of treatment, there was a relative decrease of 61% in the incidence of multiple vertebral fractures with denosumab compared with placebo (RR = 0.39, 95% CI, 0.24 to 0.63;P < 0.001) in FREEDOM.[18] There was a relative decrease of 89% in HORIZON PFT with zoledronic acid compared with placebo in patients not taking any osteoporosis medications (RR = 0.11, 95% CI, 0.05 to 0.23; P < 0.001).[19] A secondary publication of MORE reported four-year results (three years of MORE plus one-year extension) of raloxifene versus placebo for multiple vertebral fractures (RR = 0.54, 95% CI, 0.38 to 0.77; P value not reported); however, concomitant use of other bone-active agents was allowed in the extended fourth year.[25] Other raloxifene trials did not report data pertaining to this outcome.

Clinical vertebral fractures

Clinical vertebral fractures are an important and relevant outcome for which patients seek medical help. These fractures result in acute pain, decreased level of functioning, and, hence, increased health care and social costs. The between-group comparison for clinical vertebral fractures in FREEDOM resulted in a hazard ratio (HR) = 0.31 (95% CI, 0.20 to 0.47; P < 0.001).[18] As for the magnitude of the results, the absolute fracture rate was 0.8% with denosumab compared with 2.6% with placebo after 36 months of treatment. HORIZON PFT reported an HR = 0.23 (95% CI 0.14 to 0.37; P < 0.001).[19] Absolute fracture rates after 36 months were 0.5% with zoledronic acid versus 2.6% with placebo. Statistical significance was reached in both trials.

A secondary publication of MORE[24] reported a relative decrease of 41% with raloxifene compared with placebo in this trial (RR = 0.59, 95% CI 0.41 to 0.83; P not reported), while the

results from Silverman only showed a slight decrease in the relative risk of clinical vertebral fractures with raloxifene versus placebo that was not statistically significant (RR = 0.93).[23]

Hip fractures

Hip fractures are commonly considered one of the most important clinical outcomes of osteoporosis because of the associated increase in morbidity and mortality. Most patients sustaining a hip fracture are not able to return to prior level of functioning and independence, resulting in substantial social and financial costs.[1] This type of fracture typically occurs in women after the age of 70 years.[2] Results from the FREEDOM trial yielded an HR = 0.6 (95% CI, 0.37 to 0.97; P = 0.04).[18] The absolute fracture rate was 0.7% with denosumab compared with 1.2% with placebo after 36 months of treatment. HORIZON PFT reported an HR = 0.59 (95% CI, 0.42 to 0.83; P = 0.002).[19] At 36 months, the absolute fracture rate was 1.4% with zoledronic acid versus 2.5% with placebo. Statistical significance was reached in both trials.

Few data could be obtained from the included trials regarding the effect of raloxifene on hip fractures alone. MORE reported pooled hip fracture results for the two raloxifene treatment arms, one of which exceeded the recommended dosage in Canada. Therefore, this did not meet our inclusion criteria and the results were not extracted. Silverman did not address hip fractures as a separate outcome for the whole population; however, they were evaluated in a subgroup of patients at higher risk of fractures and with low femoral neck T-score ≤ -3.0 and/or presence of at least one moderate or severe vertebral fracture or multiple mild vertebral fractures at baseline. Results indicated a relative decrease of 56% in the incidence of hip fractures with raloxifene compared with placebo that was however not statistically significant (RR = 0.44; P = 0.3).[23]

Non-vertebral fractures

The importance of this outcome depends on whether it includes hip fractures, which are more serious than other non-vertebral fractures. If hip fractures are not included, other types of fractures are not usually associated with increased mortality. While the risk of fracture at all sites increases with osteoporosis, fractures at several other sites are often due to trauma and do not have similar clinical consequences. However, it was not possible to identify from HORIZON PFT and FREEDOM whether hip fractures were included. Results from FREEDOM yielded an HR = 0.8 (95% CI, 0.67 to 0.95; P = 0.01),[18] with an absolute fracture rate of 6.5% with denosumab versus 8.0% with placebo after 36 months. HORIZON PFT reported an HR = 0.75 (95% CI 0.64 to 0.87; P < 0.001).[19] Results at 36 months showed an absolute fracture rate of 8.0% with zoledronic acid versus 10.7% with placebo. Statistical significance was reached in both trials.

In MORE and Silverman, hip fractures were included as non-vertebral fractures. However, MORE did not report non-vertebral fracture results separately for each treatment arm. Consequently, no data are available for the raloxifene 60 mg group alone. Non-vertebral fractures were not assessed as a pre-specified outcome in Michalska,[22] but were nevertheless reported as adverse events at the end of an open-label extension phase after a total of 24 months of treatment. The fracture rates were low, with a total of three patients in the two groups sustaining a non-vertebral fracture. However, this method of reporting does not assess appropriately the fracture rates and limits considerably the use of these data. Results at 36 months in the Silverman trial were not statistically significant (RR = 0.94; P = 0.6).[23]

Any clinical fractures

HORIZON PFT also reported the incidence of overall clinical fractures, which included hip fractures. For this outcome, the between-group comparison resulted in a HR = 0.67 (95% CI, 0.58 to 0.77; P < 0.001, data not shown in the tables). The absolute fracture rates in the zoledronic acid and placebo groups at 36 months were 8.4% and 12.8%, respectively.[19]

Subgroup analyses

MORE[24-26] and Silverman[23] reported the effect of raloxifene versus placebo on vertebral fractures stratified into two subgroups: patients with or without prevalent vertebral fractures. Patients taking raloxifene experienced statistically significantly more benefits than placebo in both subgroups. No comparison was performed between the subgroups. Results did not reach statistical significance for patients with prevalent vertebral fractures in MORE[26] when multiple vertebral fractures were assessed, or for patients without prevalent vertebral fractures in Silverman[23] for new vertebral fractures (data not shown). Silverman reported results for hip and non-vertebral fractures according to the risk of fracture. Hip-fracture data were only provided for the high-risk subgroup and have been presented above. Results for non-vertebral fractures were consistent between raloxifene and placebo in both high-risk and lower-risk subgroups.[23]

No sub-group analyses were provided in FREEDOM, but data from a post-hoc analysis[27] were reported for a high-risk population. Denosumab significantly reduced the incidence of new vertebral fractures compared with placebo in patients with prevalent vertebral fractures (7.5% versus 16.6%, respectively, $P < 0.001$), as well as the incidence of hip fractures in patients aged ≥ 75 years (0.9% versus 2.3%, $P < 0.01$). These results were consistent with corresponding results reported for the overall FREEDOM population.

B. Health-related quality of life

FREEDOM[18] and HORIZON PFT[19] did not assess the effect of denosumab and zoledronic acid, respectively, on quality of life including pain and functional status. Among the raloxifene trials, a secondary publication of MORE stated that the treatment effect on quality of life did not differ significantly between raloxifene and placebo groups; however, no data were reported.[28]

C. Hospitalization and institutionalization

FREEDOM[18] and HORIZON PFT[19] did not assess the effect of denosumab and zoledronic acid, respectively, on hospitalizations and institutionalization. Among the raloxifene trials, Michalska[22] mentioned there were no hospitalizations due to adverse events.

D. BMD

BMD was a primary outcome in two raloxifene trials, Michalska[22] and CORE,[5] and a secondary outcome when fractures were reported. Although T-scores are commonly used in clinical practice for monitoring purposes, change in BMD does not always correlate with change in fracture risk, a clinical outcome of interest for patients, which is a complex multifactorial issue. BMD results are outlined in Table 4. In all but the Michalska trial,[22] they revealed a statistically significant difference in change in BMD from baseline to endpoint between the active treatment group and the placebo group. The relative increases show the difference in the mean percent change in BMD from baseline to endpoint between the two treatment groups; changes from baseline within each treatment group at endpoint were not reported in most publications.

Table 4: Summary of Key Efficacy Outcomes — Relative Change in BMD from Baseline to End Point Between Active Treatment and Placebo

Trial	End Point	Femoral neck			Lumbar spine			Total hip		
		Relative Increase (%)	95% CI	P value	Relative Increase (%)	95% CI	P value	Relative Increase (%)	95% CI	P value
Denosumab										
FREEDOM[18]	36 months	NR	NR	NR	9.2	8.2 to 10.1	NR	6	5.2 to 6.7	NR
Zoledronic Acid										
HORIZON PFT[19]	36 months	5.1	4.8 to 5.4	< 0.001	6.7*	5.7 to 7.7*	< 0.001*	6.0	5.8 to 6.3	< 0.001
Raloxifene										
MORE[20] **(Group 1)** †	36 months	2.10	NR	< 0.001	2.6	NR	< 0.001	NR	NR	NR
CORE[5]	7 years‡	3.0	NR	< 0.01	2.2	NR	< 0.01	NR	NR	NR
Michalska[22]	12 months	NR	NR	> 0.05	NR	NR	< 0.05	NR	NR	NR
Silverman[23]	36 months	NR	NR	NR	2.1§	NR	< 0.001	1.7§	NR	< 0.001

CI = confidence interval; NR = not reported.

* The number of patients with lumbar spine assessments was 228 in the raloxifene group and 212 with placebo. No explanations were provided.
† Study group 1: patient with T-score below –2.5 at randomization; no data for overall study population. N = 1,490 (raloxifene) versus N = 1,552 (placebo).
‡ The CORE 48-month duration was added to the MORE follow-up period and results were reported for the overall 7 years of treatment.
§ Calculated by CADTH based on change in each treatment group.

5.5 Harms outcomes

Harms outcomes with zoledronic acid and denosumab are presented in Table 5, while the corresponding data for raloxifene are presented in Table 6. The publication for the CORE trial did not report harms outcomes and therefore does not figure in the table or in the following section.

Table 5: Summary of Key Harms Outcomes for Zoledronic Acid and Denosumab

	HORIZON PFT[19] (ZOLEDRONIC ACID)			FREEDOM[18] (DENOSUMAB)		
	ZOL N = 3862	**PL N = 3852**	**P-value**	**DEN N = 3886**	**PL N = 3876**	**P-value**
	n* (%)	**n* (%)**		**n* (%)**	**n* (%)**	
Deaths	130 (3.4)	112 (2.9)	P = 0.27	70 (1.8)	90 (2.3)	P = 0.08
SAEs	1,126 (29.2)	1,158 (30.1)	P = 0.4	1,004 (25.8)	972 (25.1)	P = 0.61
AEs	**3,688 (95.5)**	**3,616 (93.9)**	**P = 0.002**	3,605 (92.8)	3607 (93.1)	P = 0.91
WDs	627 (16.1)	592 (15.3)	NR	NR	NR	NR
WDAEs[†]	80 (2.1)	70 (1.8)	P = 0.41	93 (2.4)	81 (2.1)	P = 0.39

AEs = adverse events; DEN = denosumab; NR = non-reported; PL = placebo; SAEs = serious adverse events; WDs = withdrawals; WDAEs = withdrawals for adverse events; ZOL = zoledronic acid.

* Number of patients with at least one adverse event.

† Discontinuation of follow-up or study discontinuation. Patients who discontinued a study drug but remained in the trial for follow-up are not included.

Table 6: Summary of Key Harms Outcomes* for Raloxifene									
	MORE[20†]			MICHALSKA[22]			SILVERMAN[23]		
	RAL N = 2557	PL N = 2576	P-value	RAL N = 33	PL N = 33	P-value	RAL N = 1849	PL N = 1885	P-value
	n‡ (%)	n‡ (%)		n‡ (%)	n‡ (%)		n‡ (%)	n‡ (%)	
Deaths	NR	NR	NR	NR	NR	NR	19 (1)	11 (0.6)	NR
SAEs	NR	NR	NR	NR	NR	NR	344 (19)	353 (19)	P = 0.9
AEs	NR	NR	NR	**8 (24)**	**2 (6)**	**P = 0.04**	1,775 (96)	1,813 (96)	P = 0.8
WDs	NR	652 (25)	NR	1 (2.9)	0	NR	597 (32)	629 (33)	NR
WDAEs	NR	227 (9)	NR	0	0	NR	262 (14)	240 (13)	NR
AEs=adverse events; NR = non-reported; PL=placebo; RAL=raloxifene; SAEs=serious adverse events; WDs=withdrawals; WDAEs=withdrawals for adverse events.									

* Harms outcomes were not reported for the CORE trial and, therefore, they do not figure in the table.

† The MORE publication only reported overall harms data for the two raloxifene groups pooled together (60 mg and 120 mg, which exceeds the recommended dose in Canada).

‡ Number of patients with at least one adverse event.

A. Overall harms

Mortality

The proportion of patients who died during the trials was 3.4% for zoledronic acid in HORIZON PFT[19] (2.9% with placebo) and 1.8% for denosumab in FREEDOM[18] (2.3% with placebo, Table 5), which was not significantly different to placebo in either trial. A secondary publication from MORE reported mortality rates at the end of the extension phase (four years of treatment) which were 0.9% for raloxifene compared with 1.4% for placebo.[25] The difference between the two groups was not statistically significant. In Silverman, 1.0% of patients died in the raloxifene group compared with 0.6% with placebo (Table 6).[23] Mortality was not reported for Michalska.

Serious adverse events

The incidence of serious adverse events was not significantly different in HORIZON PFT[19] and FREEDOM[18] for both zoledronic acid and denosumab versus placebo in either of the two trials. In FREEDOM, 25.8% of patients with denosumab experienced serious adverse events, including cancer, atrial fibrillation, stroke, and infection (versus 25.1% with placebo). Of note, cellulitis was more frequent with denosumab versus placebo (12 cases (0.3%) versus one case (< 0.1%), respectively; P = 0.002, data not shown).[18] In HORIZON PFT, the incidence of serious adverse events was 29.2% with zoledronic acid (versus 30.1% with placebo). Among these, atrial fibrillation was reported significantly more often with zoledronic acid versus placebo (1.3 versus 0.5%, respectively; P < 0.001, data not shown).[19] The events usually occurred more than 30 days after infusion. The between-group comparison for all serious and non-serious atrial fibrillation events did not reach statistical significance.[19]

The overall incidence of SAEs was not reported for MORE[20] and Michalska.[22] The corresponding data in Silverman were 19% for both the raloxifene and placebo groups.[23] However, there was a statistically significantly higher incidence of venous thromboembolic events, including deep vein thrombophlebitis and pulmonary embolism with raloxifene in MORE compared with placebo (1% versus 0.3%, respectively; P = 0.003). These were the only SAEs believed causally related to raloxifene treatment.[20]

Adverse events

The incidence of adverse events in patients treated with zoledronic acid was statistically significantly higher versus placebo in HORIZON PFT (95.5% versus 93.9%, respectively, P = 0.002). However, the actual difference in the incidence of adverse events between treatment arms is small (1.6%) and likely not of any clinical relevance. In FREEDOM, patients treated with denosumab had an incidence of adverse events of 92.8%, which was not significantly different from placebo (93.1%).

The overall incidence of AEs was not reported for the MORE trial.[20] There was no difference between raloxifene and placebo in Silverman, with an overall incidence of 96% in each treatment group.[23] The only statistically significant results with raloxifene were obtained in the Michalska trial, where patients with raloxifene experienced a higher incidence of adverse events (24.2% versus 6.1%, respectively; P = 0.04).[22]

Withdrawals and withdrawals for adverse events

In HORIZON PFT, results for zoledronic acid and placebo were similar in terms of overall withdrawal rates (16.1% versus 15.3%, respectively). However, these data were not reported for FREEDOM. Despite the high incidence of adverse events in both trials, discontinuation due to adverse events was low and similar between the active drug and placebo (2.1% with zoledronic acid versus 1.8% with placebo in HORIZON PFT; 2.4% with denosumab versus 2.1% with placebo in FREEDOM).

Overall discontinuation data were not reported for the raloxifene 60 mg group alone in MORE. A larger proportion of patients with placebo withdrew from the study for having multiple fractures or for excessive BMD loss (3.6% with placebo versus 1.1% with raloxifene; P < 0.001).[20] Only one patient discontinued the

Michalska trial, which occurred before any post-baseline measurements were taken, due to personal reasons.[22] Overall withdrawal rates were similar between raloxifene and placebo in Silverman[23] (32% versus 33%, respectively). The most frequent reason for discontinuation was patient request (9% in both treatment arms), while unsatisfactory efficacy was the only reason yielding a statistically significant difference between the two groups (2.1% with raloxifene versus 4.0% with placebo, respectively; P = 0.001). Withdrawals due to adverse events were similar between raloxifene and placebo (14% versus 13%, respectively).[23]

B. Harms of special interest

Three adverse events were of particular interest to our clinical review: osteonecrosis of the jaw, renal dysfunction, and atypical fractures. These will be briefly discussed below, but no further data are shown in this report.

Osteonecrosis of the jaw

No cases of osteonecrosis of the jaw (ONJ) were reported in FREEDOM[18] or in HORIZON PFT.[19] However, a specific trial database search coupled with adjudication concluded that one case (0.03%) in each treatment group was consistent with ONJ in HORIZON PFT.[19,29,30] There were no reports of cases of ONJ in the raloxifene trials.

Renal toxicity

Total renal adverse events were more frequent in the zoledronic acid group in HORIZON PFT than with placebo, but the absolute incidence was low (~ 2%).[19] More serious renal adverse events, namely renal failure and renal impairment, occurred in less than 0.5% of patients. In addition, there was no significant difference between the groups in the proportion of patients with urinary protein levels > 2+ or with creatinine clearance < 30 ml/minute at the end of the trial,[19] suggesting that patients did not appear to experience a higher level of renal dysfunction compared with placebo. The incidence of renal adverse events was not specifically reported for FREEDOM. Nevertheless, acute prerenal failure and renal impairment were reported to be present in less than < 1% of the trial population. In MORE, the incidence of adverse events related to kidney disease was lower in the raloxifene group compared with placebo (0.39% versus 1.13%, respectively, HR = 0.37, 95% CI 0.18 to 0.77).[31] Other raloxifene trials did not report results for renal adverse events.

Atypical bone response

Atypical fractures are very uncommon and are part of an atypical bone response that may theoretically be related to suppression of bone turnover.[32] While no atypical fractures were observed with denosumab in FREEDOM,[18] there were three cases in the placebo group. Only one non-union of fracture was reported in the trial, in the placebo group. The incidence of delayed fracture healing was also lower with denosumab versus placebo (0.05% versus 0.10%, respectively; P not reported). In HORIZON PFT, no statistically significant difference was seen between zoledronic acid and placebo in terms of patients suffering from atypical fractures.[33] Very few patients experienced the non-union of a fracture during the trial.[19] No patients reported adverse events related to fracture healing.[19] There were no reports of adverse events related to atypical fractures among the raloxifene trials.

Other adverse events

Other adverse events results worth mentioning include no statistically significant difference in the incidence of cancer and infection in FREEDOM.[18] In HORIZON PFT,[19] patients receiving zoledronic acid infusions experienced a higher incidence of arrhythmia (7% versus 5%, respectively; P = 0.003), as well as post-dose symptoms such as pyrexia (16% versus 2%), myalgia (10% versus 2%), influenza-like symptoms (8% versus 2%), headaches (7% versus 2%), and arthralgia (6% versus 2%; P < 0.001 for all comparisons). However, the incidence of post-dose symptoms with zoledronic acid decreased over time, from 32% after the first infusion to 7% after the second infusion to 3% after the third infusion, although it remained higher than the corresponding incidence of 6%, 2%, and 1% with placebo (P < 0.001 for all three comparisons).[19] Patients treated with raloxifene in both MORE[20] and Silverman[23] experienced more vasodilation/hot

flashes and leg cramps than placebo. The incidence of hot flashes with raloxifene versus placebo was 10% versus 6%, respectively, for MORE, and 12% versus 6% for Silverman, while the incidence of leg cramps was 7% versus 4% for MORE and 12% versus 8% for Silverman ($P \leq 0.001$ for all comparisons).

6 DISCUSSION

6.1 Summary of Evidence

We identified six RCTs, whose results were reported in 20 published articles assessing the efficacy and safety of denosumab (one RCT), zoledronic acid (one RCT), or raloxifene (four RCTs) in the treatment of postmenopausal women with osteoporosis. No active-controlled RCTs were identified in the literature search; only placebo-controlled RCTs were retrieved. Therefore, no direct treatment comparisons were available to assess the relative efficacy of the drugs. We considered, but elected not to perform, indirect comparisons between the trials, considering substantial heterogeneity in patient populations and significant challenges limiting the use of statistical adjustments to manage heterogeneity, which were beyond the scope of this report.

6.2 Interpretation of the results

Efficacy

The current evidence revealed that denosumab, zoledronic acid, and raloxifene were all effective in reducing the risk of vertebral fractures, both clinically- and radiographically-assessed (morphometric), after 36 months of treatment compared with placebo. Denosumab and zoledronic acid reduced the risk of multiple vertebral fractures, hip fractures, and non-vertebral fractures. The included trials only provided limited evidence regarding the effect of raloxifene at the recommended dose of 60 mg daily on these outcomes, which suggested that it may not be effective in preventing non-vertebral fractures, including hip fractures.

Pooled data for the two raloxifene doses in the MORE trial were not considered in our review since they did not meet our inclusion criteria. However, the results for these types of fractures were not significantly different from placebo, although a large proportion of the patients contributing to the results for raloxifene received twice the recommended dose.[20] Such a conclusion is consistent with other literature indicating that raloxifene has not been shown to reduce non-vertebral fractures.[4]

Denosumab, zoledronic acid, and raloxifene were each associated with an increase in BMD compared with placebo after 36 months of treatment and up to seven years in one trial for raloxifene.[5] Nevertheless, the clinical relevance of these findings remains uncertain. Although T-scores are commonly used in clinical practice for monitoring purposes, change in BMD does not always correlate with change in fracture risk, which is a complex multifactorial issue. Therefore, clinical patient outcomes such as fractures are preferred to assess the efficacy of osteoporosis agents. The evidence for health-related quality of life and hospitalizations/long-term care needs was not sufficient to assess the effect of denosumab, zoledronic acid, or raloxifene on these outcomes.

Harms

The proportion of patients who died during the trials, as well as the overall incidence of serious adverse events, was not significantly different between each active drug and placebo. Nevertheless, some specific toxicities were reported more frequently with denosumab, zoledronic acid, or raloxifene. In the included trials, denosumab was associated with a higher incidence of cellulitis, zoledronic acid with atrial fibrillation, and raloxifene with venous thromboembolism and hot flushes compared with placebo. While thromboembolic events have been established as a major concern with the use of raloxifene,[4,6] additional data regarding atrial fibrillation with zoledronic acid suggest that they may have been false signals. Indeed, this finding was not observed consistently in other zoledronic acid trials,[7] and in HORIZON PFT the events usually occurred more than 30 days after administration of the drug, suggesting they may not have been related to the infusion.[19] A review of safety data by the FDA confirmed that, across all studies, no clear

association between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation was observed therefore health-care professionals should not alter prescribing patterns.[8]

The incidence of ONJ and atypical fractures was low and not significantly different between the active drugs and placebo in the trials. Nevertheless, ONJ has been previously reported with bisphosphonates in postmenopausal osteoporosis, and more frequently with high doses of intravenous bisphosphonates in cancer patients.[32] The role of bisphosphonates in the occurrence of atypical fractures cannot be ruled out, although causality remains unclear.[7] Despite no evidence of renal toxicity in HORIZON PFT, zoledronic acid has been associated with renal dysfunction and therefore should not be used in patients with severe renal impairment and be used with caution in the presence of other products that could impact renal function.[7]ONJ, atypical fractures, and renal dysfunction are uncommon adverse events and, as a result, the findings from the included trials should not exclude a potential relationship with the active drugs. The specific harms profiles should be considered when making a treatment decision. Additional potential benefits should also be weighted. For instance, raloxifene is also associated with a reduced incidence of invasive breast cancer,[4,34] which may be desirable to some patients.

6.3 Limitations

The current evidence was limited to a total of six placebo-controlled RCTs. Although we searched for trials comparing denosumab, zoledronic acid, and raloxifene with each other, no active-controlled RCTs were identified in the literature search. Therefore, no direct treatment comparisons were available to assess the relative efficacy of the drugs. First line therapy is oral bisphosphonate. This review focused on second-line treatment options for postmenopausal women with osteoporosis. In clinical practice, denosumab, raloxifene and zoledronic acid are all used as options following an inadequate response or intolerance to oral bisphosphonates. Heterogeneity exists among the trial populations, especially with regard to the risk of fracture. Indeed, patients in the denosumab and zoledronic acid trials were older and their BMD measurement appeared slightly lower than those of the patients in the raloxifene trials. While patients in the denosumab trial were less likely to have a prevalent fracture at baseline, the corresponding proportion was the highest in the zoledronic acid study, with marked variations existing for the raloxifene trials. As a result, we considered, but elected not to perform, indirect comparisons between the trials: there were significant challenges limiting the use of statistical adjustments to manage heterogeneity, which were beyond the scope of this report. In addition, the validity of these adjustments would have been limited by the low number of studies retrieved in light of our research question.

Despite some variation in the quality of the included trials, most of them showed an acceptable degree of methodological rigour. There were, however, some quality concerns, such as insufficient reporting to allow adequate judgment on allocation sequence and concealment, blindness of patients and investigators, as well as patient withdrawals. The trials were usually representative of the Canadian population of women living with osteoporosis; except for the exclusion of patients with recent bisphosphonates experience (oral bisphosphonates are widely used in clinical practice). In addition, we could not find any trials evaluating the efficacy and harms of denosumab, zoledronic acid, and raloxifene as a second-line treatment option for postmenopausal women with intolerance or inadequate response to oral bisphosphonates, although these treatment options may be used in clinical practice in this indication. These limitations may weaken to some extent the strength of evidence regarding the effectiveness of denosumab, zoledronic acid, and raloxifene in postmenopausal women with osteoporosis.

6.4 Comparison with other literature

No active-controlled RCTs were identified in the literature search; i.e., no direct treatment comparisons were available to assess the relative

efficacy of the drugs. A systematic review recently published by Hopkins et al.[35] attempted to address this evidence gap through an indirect comparison of nine osteoporosis drugs, including those drugs reviewed in this report. Based on the combination of effect size, and probability of being most efficacious (based on an unadjusted statistical analysis), teriparatide, zoledronic acid, and denosumab ranked highest for reducing non-vertebral and vertebral fractures.[35] The authors highlighted some important limitations regarding their analysis and conclusions. They stated that statistical adjustments were important to explore due to the existence of key differences in patient characteristics across trials, which might have affected estimates of the comparative effectiveness among treatments in the analysis. These differences pertain to particularly important factors, including age, bone mineral density, and history of vertebral fracture. However, the modeling required for exploring statistical adjustments was not possible due to the low number of studies for each drug, and it is therefore unclear whether the estimates of effectiveness are robust.

In addition, the authors raised concerns regarding the results for etidronate. In their analysis, this drug had a high probability of being the most efficacious treatment, which is contrary to other evidence.[35]Therefore, the results from Hopkins et al. should be interpreted with caution.

7 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Six placebo-controlled RCTs were included in this systematic review, assessing the efficacy and safety of denosumab, zoledronic acid, and raloxifene in the treatment of postmenopausal women with osteoporosis. No direct comparison between these drugs was identified. Denosumab and zoledronic acid both reduced the risk of vertebral, hip, and non-vertebral fractures. While raloxifene was associated with a reduced incidence of vertebral fractures, the included trials only provided limited evidence regarding hip and non-vertebral fractures, although these fractures have clinically important consequences. The results suggest that raloxifene may not be effective in preventing hip and non-vertebral fractures, which is consistent with other reports.[4] We considered, but elected not to perform, indirect comparisons between the trials: significant challenges limited the use of statistical adjustments to manage heterogeneity, which were beyond the scope of this report. Therefore, the characteristics of each trial population should be considered when making a treatment decision. All three drugs were associated with a relative increase in BMD compared with placebo, but the clinical relevance of this is uncertain because changes in BMD do not always correlate with changes in fracture risk.

Mortality data and the incidence of serious adverse events did not raise new safety concerns. Nevertheless, some specific toxicities were reported more frequently with denosumab, zoledronic acid, or raloxifene (than placebo) and, therefore, specific harms profiles should be considered in the selection of these agents.

No evidence was identified to evaluate the efficacy and harms of these drugs as a second-line treatment option for postmenopausal women with intolerance or inadequate response to oral bisphosphonates, although this population may be prescribed these medications.

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APPENDICES

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE <1996 to 2011 Week 21> Ovid Medline <1948 to May Week 3 2011> Ovid Medline In-Process & Other Non-Indexed Citations <December 13, 2006> **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 27, 2011
Alerts:	Monthly search updates began May 27, 2011and ran until October 2011.
Study Types:	Systematic reviews; meta-analyses; technology assessments; and randomized controlled trials
Limits:	Publication years: Raloxifene 2001-May 2011 Denosumab 2010 – May 2011 Zoledronic acid 2007 – May 2011 Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ot	At the end of a phrase, searches the phrase, other title
.em	Entry month (for the Embase database)
.ed	Entry date (for the Medline database)
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

.nm Substance name

Multi-database Strategy

Embase, Ovid MEDLINE(R)

#	Searches	Results
1	(20109* or 201010* or 201011* or 201012* or 2011*).ed.	862292
2	denosumab.nm. or 615258-40-7.rn.	1383
3	(prolia* or denosumab* or AMG162 or AMG 162 or Xgeva*).ti,ot,ab,sh,rn,hw,nm.	1756
4	(2 or 3) and 1	127
5	("200712" or 2008* or 2009* or 2010* or 2011*).ed.	3315019
6	zoledronic acid.nm. or 118072-93-8.rn.	7364
7	(Aclasta or Reclast or zoledronate or zometa or zoledronic or CGP 42446 or cgp42446 or zol446 or zol 446).ti,ot,ab,sh,rn,hw,nm.	8643
8	(6 or 7) and 5	1100
9	(2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011*).ed.	8295241
10	exp Raloxifene/ or 84449 90 1.rn.	9509
11	(Raloxifene or Keoxifene or Evista or LY156758).ti,ot,ab,sh,rn,hw,nm.	10501
12	(10 or 11) and 9	2301
13	exp osteoporosis/ or exp Osteoporosis, Postmenopausal/ or exp Bone Demineralization, Pathologic/	94496
14	(osteoporosis* or osteoporotic or osteolysis or Perimenopaus* or post-menopaus* or postmenopaus* or porous bones).ti,ot,ab,sh,hw.	212212
15	((Bone or bones) adj2 (loss* or atrophy or density or regeneration or demineralization or mineralization or porous or porousness)).ti,ot,ab,sh,hw.	143292
16	(osteoporo* adj1 (primary or secondary or "type 1" or "type 2" or "T1" or "T2" or steroid induced or glucocorticoid induced or "SIOP" or "GIOP")).ti,ot,ab,sh,hw.	3458
17	or/13-16	291526
18	(4 or 8 or 12) and 17	2376
19	exp animals/	16170068
20	exp animal experimentation/	734988
21	exp models animal/	829632
22	exp animal experiment/	734988
23	nonhuman/	2299256
24	exp vertebrate/	23535004
25	animal.po.	0
26	or/19-25	24740291

27	exp humans/	18916077
28	exp human experiment/	160860
29	human.po.	0
30	or/27-29	18916322
31	26 not 30	5824187
32	meta-analysis.pt.	30081
33	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/	132157
34	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.	75269
35	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.	7890
36	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.	14985
37	(data synthes* or data extraction* or data abstraction*).ti,ab.	20645
38	(handsearch* or hand search*).ti,ab.	8420
39	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.	18813
40	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.	4321
41	(meta regression* or metaregression* or mega regression*).ti,ab.	2877
42	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	184074
43	(medline or Cochrane or pubmed or medlars).ti,ab,hw.	128427
44	(cochrane or health technology assessment or evidence report).jw.	20508
45	(meta-analysis or systematic review).md.	0
46	or/32-45	309080
47	Randomized Controlled Trial.pt.	314391
48	Randomized Controlled Trials as Topic/	81166
49	Randomized Controlled Trial/	550117
50	Randomization/	116154
51	Random Allocation/	116154
52	Double-Blind Method/	185014
53	Double Blind Procedure/	72985
54	Double-Blind Studies/	168335
55	Single-Blind Method/	27744
56	Single Blind Procedure/	12382
57	Single-Blind Studies/	27744

58	Placebos/	164696
59	Placebo/	134654
60	(random* or sham or placebo*).ti,ab,hw.	1512199
61	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	265356
62	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	499
63	or/47-62	1540672
64	18 and (46 or 63)	879
65	64 not 31	802
66	("201036" or "201037" or "201038" or "201039" or 20104* or 20105* or 2011*).em.	1772381
67	*denosumab/	340
68	(prolia* or denosumab* or AMG162 or AMG 162 or Xgeva*).ti,ab.	892
69	(68 or 67) and 66	338
70	("200749" or "200750" or "200751" or "200752" or 2008* or 2009* or 2010* or "2011").em.	5546198
71	*zoledronic acid/	1875
72	(Aclasta or Reclast or zoledronate or zometa or zoledronic or CGP 42446 or cgp42446 or zol446 or zol 446).ti,ab.	4440
73	(71 or 72) and 70	2104
74	(2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011*).em.	16871214
75	*raloxifene/	3149
76	(Raloxifene or Keoxifene or Evista or LY156758).ti,ab.	5119
77	(75 or 76) and 74	4695
78	osteoporosis/ or postmenopause osteoporosis/ or bone demineralization/	84431
79	(osteoporosis* or osteoporotic or osteolysis or Perimenopaus* or post-menopaus* or postmenopaus* or porous bones).ti,ab.	154917
80	((Bone or bones) adj2 (loss* or atrophy or density or regeneration or demineralization or mineralization or porous or porousness)).ti,ab.	93099
81	(osteoporo* adj1 (primary or secondary or "type 1" or "type 2" or "T1" or "T2" or steroid induced or glucocorticoid induced or "SIOP" or "GIOP")).ti,ab.	3334
82	or/78-81	234627
83	(69 or 73 or 77) and 82	4079
84	83 and (46 or 63)	1950
85	84 not 31	1810
86	85 use emef	1177
87	65 use pmez	802
88	86 or 87	1979

89	remove duplicates from 88	1363
90	conference abstract.pt.	472305
91	89 not 90	1218

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

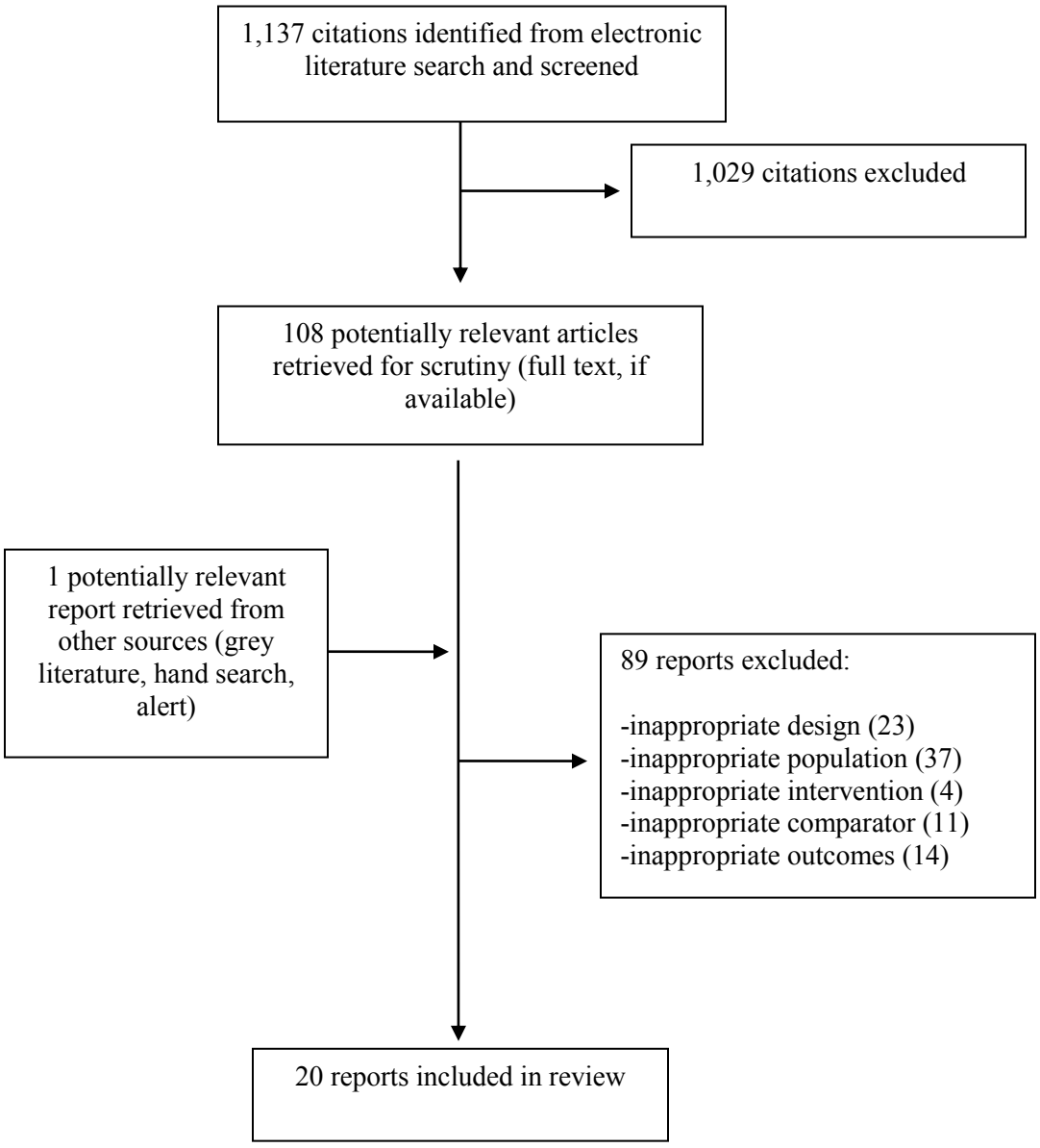
Grey Literature

Dates for Search:	May 28-June 6, 2011
Keywords:	Included terms for Osteoporosis, Zoledronic Acid, Denosumab, Raloxifene
Limits:	Publication years: Raloxifene 2001 – May 2011 Denosumab 2010 – May 2011 Zoledronic acid 2007 – May 2011

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (http://www.cadth.ca/resources/grey-matters) were searched:

- health technology assessment agencies
- databases (free)
- internet search
- open access journals
- drug and device regulatory approvals
- drug class reviews
- advisories and warnings.

APPENDIX 2: SELECTION OF INCLUDED STUDIES



APPENDIX 3: SUMMARY OF STUDY CHARACTERISTICS OF INCLUDED STUDIES

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
DENOSUMAB				
FREEDOM International, multicentre, placebo-controlled, DB RCT Cummings 2009[18] Jamal 2011[36] N = 7,868 enrolled (number of patients who completed the study not reported)	Postmenopausal women with osteoporosis between 60 and 90 years with a T-score between -2.5 and -4 at lumbar spine or total hip. Use within 12 months or lifetime use > 3 years of bisphosphonates was not allowed. Patients with any severe fracture or > 2 moderate prevalent vertebral fractures were excluded.	**Denosumab** (n = 3,902) SC injection of 60 mg every 6 months **Placebo** (n = 3,906) SC injection every 6 months **Other medication:** Daily calcium (≥1000 mg) supplementation. Daily vitamin D (≥400 UI) supplementation if required. **Duration:** 36 months	**Primary efficacy:** New vertebral fractures (as assessed centrally using a semi-quantitative grading scale on annually-taken lateral spine radiographs). **Secondary efficacy:** Time to first non-vertebral and hip fractures, as well as BMD. **Harms:** AEs, SAEs, deaths, WDs, WDEAs.	Manufacturer-funded. Fractures of skull, face, mandible, metacarpals, fingers, or toes were excluded, as they are not associated with low BMD. Discontinuation from the study was required if total hip BMD ↓ by > 7% over 12 months or by ≥ 10% during the study, or if T-score was < –4.0.
ZOLEDRONIC ACID				
HORIZON PFT International, multicentre, placebo-controlled, DB RCT Black 2007[19] Secondary publications: Boonen 2008[37] Grbic 2008[29] Grbic 2010[30] Reid 2010[38] Black 2010[33]	Postmenopausal women with osteoporosis between 65 and 89 years with a T-score ≤ –2.5 at the femoral neck, or with a T-score ≤ –1.5 and at least 2 mild vertebral fractures or 1 moderate vertebral fracture. Previous use of bisphosphonates allowed with washout period, which was dependent on duration of previous use. Concomitant use of some osteoporosis medication allowed, including	**Zoledronic acid** (n = 3,889) 5 mg IV at baseline, 12 months and 24 months **Placebo** (n = 3,876) IV administration at baseline, 12 months and 24 months **Other medication:** Daily calcium (1,000-1,500 mg) and vitamin D (400-1,200 IU) supplementation. **Duration:** 36 months	**Primary efficacy:** New vertebral fractures in patients not taking osteoporosis medication at randomization (as assessed centrally using quantitative morphometry and standard methods on annually-taken lateral spine radiographs). Hip fractures in the whole patient population. **Secondary efficacy:** Non-vertebral fractures, clinical fractures, change in BMD.	Manufacturer-funded. Fractures of toe, facial bone, finger, and excessive trauma fractures excluded. Patients who took allowed medication were placed in strata 2 (n = 1,652), while patients in strata 1 did not take any osteoporosis medication (n = 6,113). Discontinuation from the

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
n = 18,421 screened N = 7,765 randomized N = 5,975 completed study (77%)	HRT, raloxifene, and calcitonin.		**Harms:** AEs, SAEs, deaths, WDs, WDEAs.	study was required if BMD ↓ by > 8% at year 1 or 10% at year 2.
RALOXIFENE				

MORE
International, multicentre, placebo-controlled, DB RCT
 	
Ettinger 1999[20]
Secondary publications:
Siris 2002[26]
Delmas 2002[25]
Maricic 2002[24]
Barrett-Connor 2002[39]
Qu 2005[40]
Oleksik 2005[28]
Melamed 2011[31]
 	
N = 22,379 screened
N = 7,705 randomized
N = 5,692 completed (74%)
	Postmenopausal women with osteoporosis with:
	• A T-score ≤ -2.5 at the femoral neck or lumbar spine, or
	• Low BMD plus:
	  ○ at least 1 moderate or severe vertebral fracture or
	  ○ at least 2 mild vertebral fractures, or
	• At least 2 moderate fractures regardless of BMD.
	
	Use of bisphosphonates within the previous 6 months was not allowed.
		Raloxifene 60 mg PO daily (n = 2557)
		Raloxifene 120 mg* PO daily (n = 2572)
		Placebo (n = 2576)
		
		Other medication:
		Daily calcium (500 mg) and vitamin D (400-600 IU) supplementation.
		
		Duration: 36 months
		(in addition to a 12-month extension period where bone-active medications were allowed)
			Efficacy:
			Incident vertebral fractures, as assessed centrally using a semi-quantitative scale on vertebral radiographs.
			Non-vertebral fractures, determined by direct questioning.
			BMD.
			
			Harms:
			AEs, SAEs, deaths.
				Manufacturer-funded.
				
				Fractures resulting from traffic collision, assault, falling, or moving object are considered traumatic and, hence, excluded.
				
				Discontinuation from the study was required if:
				• BMD ↓ ≥ 7% at lumbar spine or 10% at femoral neck at yr 1.
				• BMD ↓ ≥ 11% at lumbar spine or 14% at femoral neck (yr 2).
				• Patients experienced > 2 incident vertebral fractures.

CORE International, multicentre, placebo-controlled, DB RCT Siris 2005[5] N = 4,011 enrolled in	Postmenopausal women with osteoporosis who participated in the MORE study. <u>CORE BMD sub-study:</u> Patients from the U.S. sites who had a valid BMD measurement at year 3, who	<u>CORE BMD sub-study:</u> **Raloxifene 60 mg PO daily** (n = 259) **Placebo** (n = 127) **Other medication:** Daily calcium (500 mg) and vitamin D (400-600 IU)	<u>CORE BMD sub-study:</u> **Efficacy:** BMD (lumbar spine and femoral neck). **Harms:** Harms outcomes are not reported for this particular subset of the	Manufacturer-funded. CORE was the continuation from the MORE trial and was designed to assess the effects of raloxifene on breast cancer for four additional years beyond MORE. Focus will be given

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
CORE <u>BMD sub-study:</u> N = 844 enrolled N = 386 analyzed N completed not reported	were at least 80% compliant with study medication and who did not take any other bone-active agents.	supplementation. **Duration:** 48 months (BMD outcome was reported for 7 years, i.e. 48 months in MORE and 36 months in CORE)	population.	here to the CORE BMD sub-study.
Michalska Single-centre, placebo-controlled DB RCT with an open-label active-controlled arm Michalska 2006[22] N = 125 screened N = 100 enrolled N = 99 randomized N = 99 completed (100%)	Postmenopausal women with osteoporosis between 50 and 80 years treated with alendronate 10mg/day for >3 years with a T-score <-2.5 at the lumbar spine or proximal femur before initiation of alendronate. **All patients had previous bisphosphonate experience.** Use of medication that might influence bone turnover was not allowed.	**Raloxifene 60 mg PO daily** (n = 33) **DB Raloxifene Placebo** (n = 33) **O/L Alendronate 10 mg PO daily** (n = 33) **Other medication:** Daily calcium (500 mg) and vitamin D (800 IU) supplementation. **Duration:** 12 months	**Primary efficacy:** BMD (change from baseline in vertebral BMD after 12 months within and between groups). **Secondary efficacy:** BMD (change in total hip and femoral neck BMD between groups). **Harms:** AEs, WDEAs.	Not manufacturer-funded. Double-blind medication was provided by Eli Lilly. Michalska is the only trial included in this review with a population of post-menopausal women with osteoporosis being systematically treated with a bisphosphonate immediately prior to the start of the trial.
Silverman International, multicentre, placebo-controlled and active-controlled DB RCT Silverman 2008[23] Christiansen 2010[41] N = 26,749 screened N = 7,492 randomized N = 6,847 analyzed	Postmenopausal women with osteoporosis between 55 and 85 years with a T-score between -2.5 and -4 at lumbar spine or femoral neck, or with at least one mild radiographically-confirmed vertebral fracture. Use of bisphosphonates and other osteoporosis treatments was prohibited within six months of screening.	**Bazedoxifene[†] 20 mg PO daily** (n = 1886) **Bazedoxifene[†] 40 mg PO daily** (n = 1872) **Raloxifene 60 mg PO daily** (n = 1849) **Placebo** (n = 1885) **Other medication:** Daily supplementation with calcium (up to 1200 mg) and vitamin D (400-800 IU).	**Primary efficacy:** New vertebral fracture (incidence of radiographically-confirmed fractures after 36 months). **Secondary efficacy:** Clinical vertebral fractures. Non-vertebral fractures. BMD (change from baseline in lumbar spine, total hip and femoral neck). **Harms:**	Manufacturer-funded.

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
N = 4,991 completed (67%)		**Duration:** 36 months	AEs, SAEs, deaths, WDs, WDEAs.	

AE = adverse event; BMD = bone mineral density; DB = double-blind; HRT = hormone replacement therapy; IV = intravenous; O/L = open-label; PO = orally; RCT = randomized controlled trial; SAE = serious adverse event; WD = withdrawal; WDAE = withdrawal due to AE.

* Raloxifene 120 mg exceeds the recommended dosage in Canada.

† Bazedoxifene is not approved in Canada. For both, only the raloxifene 60 mg treatment groups are of interest to this review.

APPENDIX 4: SUMMARY OF RELEVANT PATIENT POPULATION AND BASELINE CHARACTERISTICS

STUDY NAME	AGE				T-SCORE			PREVALENT FRACTURES (FX)			PRIOR USE OF BISPHOSPHONATES		
	Age (Mean ± SD)		Years Since Menopause		Inclusion Criteria	Baseline Data (Mean ± SD)		Inclusion Criteria	Baseline Data (% prevalent Fx)		Inclusion Criteria	Baseline Data (% treatment-experienced)	
	Active	PL	Active	PL		Active	PL		Active	PL		Active	PL
DENOSUMAB													
FREEDOM[18,36]	72.3 (5.2)	72.3 (5.2)	NR	NR	T-score between -2.5 and -4 at LS or TH	At LS: -2.82 (0.70) At FN: -2.15 (0.72)	At LS: -2.84 (0.69) At FN: -2.17 (0.71)	≤ 2 moderate Fx allowed. No severe	23.8%	23.4%	Prohibited within 12 months	NR	
ZOLEDRONIC ACID													
HORIZON PFT[19,29,30,33,37,38]	73.1 (5.3)	73 (5.4)	NR	NR	• ≤ -2.5 – no Fx; • ≤ -1.5 with Fx; at FN only	73% of patients < -2.5	71% of patients < -2.5	Yes	62.3%	64.2%	Washout period required	14.6%	14.4%
RALOXIFENE													
MORE[20,24-26,28,31,39,40]*	66.4 (6.9)	66.6 (7)	18.6 (8.5)	18.7 (8.3)	• ≤ -2.5 – no Fx; • Low BMD with Fx;	At LS: -2.55 (1.09) At FN:	At LS: -2.58 (1.14) AT FN:	Yes	37.9%	36.4%	Prohibited within 6 months	NR	

STUDY NAME	AGE				T-SCORE			PREVALENT FRACTURES (FX)			PRIOR USE OF BISPHOSPHONATES		
	Age (Mean ± SD)		Years Since Menopause		Inclusion Criteria	Baseline Data (Mean ± SD)		Inclusion Criteria	Baseline Data (% prevalent Fx)		Inclusion Criteria	Baseline Data (% treatment-experienced)	
	Active	PL	Active	PL		Active	PL		Active	PL		Active	PL
					• ≥ 2 Fx regard-less of BMD; at FN or LS	-2.32 (0.55)	-2.33 (0.55)						
CORE (BMD sub-study)[5†]	66.7 (6.9)	67.5 (7)	NR	NR		AT LS: -2.18 (1.03) At FN: -2.25 (0.43)	AT LS: -2.17 (0.95) At FN: -2.23 (0.43)		26%	27%			
Michalska[22]	65.6 (7.1)	64.5 (6.3)	19.5 (7.9)	16.0 (6.0)	<- 2.5 at LS or proximal femur	NR		NA	NR		Required	100%	
Silverman[23,41]	66.4 (6.7)	66.5 (6.8)	19.5 (8.7)	19.5 (8.8)	• Between -2.5 and -4 at LS or FN (no Fx); • Vertebral Fx regardless of BMD	At: LS: -2.4 (1.2) At FN: -1.7 (0.9)	At LS: -2.4 (1.2) At FN: -1.8 (0.9)	Yes	56.3%	56.4%	Prohibited within 6 months	NR	

FN = femoral neck; Fx = fracture; LS = lumbar spine NA = not addressed; NR = not reported; PL = placebo; SD = standard deviation; TH = total hip.

* Baseline data from Delmas, which reported the four-year results of MORE † Subset of CORE, in which patients did not use other bone-active agents.

APPENDIX 5: CRITICAL APPRAISAL OF INDIVIDUAL STUDIES

Study Year, Country	Study Design, Setting	Study Strengths	Study Limitations
FREEDOM [18,36] 2009, 2011 International	RCT Study sites (hospital)	Patients were randomized. Baseline characteristics were balanced across treatment groups. Bisphosphonate use was prohibited within the prior 12 months, which is appropriate considering the residual effect of the drugs on the bone. Appropriate methods were used to assess trial outcomes: radiographs for vertebral fractures assessment and diagnostic imaging for clinical fractures confirmation. Analyses of efficacy were performed using an intention to treat methodology, considered a conservative approach. **External validity:** FREEDOM addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D, a recommended approach to maximize treatment effect representative of clinical practice.	Information was insufficient to allow judgment on allocation sequence and concealment. Blindness of investigators, patients, and study monitors was not addressed in the publication. Although blinding was less likely to influence objective outcomes such as BMD, it is important for subjective evaluations such as vertebral fractures assessed through radiographs. Patient withdrawal was not reported. However, high or unbalanced discontinuation may affect internal validity. Discontinuation from the study was required for patients with substantial decrease in BMD, which was more likely to happen in the placebo arm. **External validity:** Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population.
HORIZON PFT [19,29,30,33,37,38] 2007, 2008, 2010 International	RCT Study sites (hospital)	Reference to a double-blind design for blindness of investigators and patients. Patients were randomized and the allocation sequence seems adequately generated. Baseline characteristics were balanced across treatment arms. A washout period was required for patients who were previously treated with oral bisphosphonates. Appropriate methods were used to assess trial outcomes with radiographs for vertebral fractures assessment. The proportion of patients withdrawing over the trial was acceptable (16%), and appeared balanced between treatment arms. Analyses of efficacy were performed using the conservative intention to treat analysis approach.	Information was insufficient to allow judgment on allocation concealment and blinding of the evaluator to treatment groups. Concomitant use of some osteoporosis medication was allowed, which is a confoundant. However, 79% of patients did not take any medication and vertebral fractures were assessed in this population only. Reasons for discontinuation were not reported. Discontinuation from the study was required for patients with substantial decrease in BMD, which was more likely to happen in the placebo arm.

Study Year, Country	Study Design, Setting	Study Strengths	Study Limitations
		External validity: HORIZON PFT addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D.	**External validity:** Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population.
MORE[20,24-26,28,31,39,40] 1999, 2002, 2005, 2011 International	RCT Study sites (hospital)	Use of identical pills to address blindness of investigators and patients. Patients were randomized. Baseline characteristics were balanced across treatment arms. Appropriate methods were used to assess trial outcomes with radiographs for vertebral fractures assessment, which were performed centrally by radiologists blinded to treatment groups. Withdrawals were acceptable and seemed balanced between the placebo and the pooled raloxifene treatment arms. Some reasons for discontinuation were reported separately in a secondary publication, including patients with substantial BMD decrease. All analyses were performed using an intention-to-treat approach. Missing post-baseline data were imputed by carrying forward the last observation. **External validity:** HORIZON PFT addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D.	Information was insufficient to allow judgment on allocation sequence and concealment. Clinical fractures were assessed by questionnaire (no confirmation with diagnostic imaging mentioned). Overall discontinuation data were pooled for the two raloxifene groups; however, only the 60 mg treatment arm is relevant. In a secondary publication, withdrawals were unequal in terms of reason for discontinuation, with > 3 times more patients in the placebo group experiencing excessive BMD decrease or multiple fractures compared with raloxifene. **External validity:** Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population. Patients from one of the three treatment arms received raloxifene 120 mg daily, which exceeds the recommended dosage in Canada. This is not an appropriate comparator and as a result, these data were not extracted.
CORE[5] 2005 International	RCT Study sites (hospital)	CORE is the continuation from the MORE trial. The article indicated that all CORE participants and investigators remained blinded to treatment assignment from the beginning of MORE to the end of the CORE trial. Baseline characteristics were balanced across treatment arms. Appropriate methods were used to assess BMD.	CORE is the continuation from MORE and assessed the effect of raloxifene on breast cancer. The CORE BMD sub-study provided data with regard to change in BMD. Clinical fractures were assessed for the whole population as a secondary outcome. However, major limitations prevented the use of CORE fracture data in our review. These limitations include inadequate fracture assessment resulting in substantial underestimation of fracture rates, as well as

Study Year, Country	Study Design, Setting	Study Strengths	Study Limitations
		External validity: CORE addresses a clear and appropriate research question. Although the primary outcome is not relevant to the review, a BMD sub-study assessed change in BMD in a subset of the population consistent with our selection criteria.	allowing the use of concomitant additional bone-active agents such as bisphosphonates, calcitonin, hormones, and SERMs, which is a significant confoundant. Randomization was performed at the beginning of the MORE trial and only a subset of patients fulfilling specified criteria after three years of treatment were included in the CORE BMD sub-study. This is not considered effective to ensure between-group similarity, especially regarding unreported or potentially unidentified confounding factors. The proportion of patients withdrawing over the trial was not reported nor was the methodology used to perform analyses of efficacy. **External validity:** The CORE BMD sub-study provided data with regard to change in BMD. However, this is a surrogate outcome that does not always correlate with change in fracture risk. Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population.
Michalska[22] 2006 Austria	RCT Hospital clinic	Reference to a double-blind design and to the use of identical pills for blindness of investigators and patients. Patients were randomized. Baseline characteristics were balanced between the raloxifene and placebo groups. BMD was appropriately measured by densitometry. All randomized patients completed the trial. Analyses of efficacy were performed using a modified intention to treat approach to include all patients who received at least one dose of the study drug, had a baseline measurement and at least one post-treatment observation. Michalska is the only trial included in the systematic review that is not manufacturer-funded; however, medication was provided	Information was insufficient to allow judgment on allocation sequence and concealment. **External validity:** The trial evaluated change in BMD. However, this is a surrogate outcome that does not always correlate with change in fracture risk. Michalska is the only trial included in this review where bisphosphonate treatment was required immediately prior to enrolment. Long-term residual effect of the bisphosphonate is likely to prevent bone resorption and, hence, preclude BMD decrease from resuming. This leads to overestimation of the efficacy of subsequent antiresorptive treatments. In addition, the reasons for switching from a bisphosphonate to

Study Year, Country	Study Design, Setting	Study Strengths	Study Limitations
		by the pharmaceutical company. **External validity:** Michalska addresses a clear and appropriate research question. Patients were supplemented with calcium and vitamin D.	raloxifene, an agent known for a less marked antiresorptive effect, were not reported. Patients from one of the three treatment arms received alendronate, which was not selected as a comparator in our protocol. As a result, data from this treatment group were not extracted.
Silverman[23,41] 2008 International	RCT Study sites (hospital)	Reference to a double-blind design for blindness of investigators and patients. Patients were randomized and the allocation sequence seems adequately generated. Baseline characteristics were balanced across treatment arms. Appropriate methods were used to assess trial outcomes with radiographs for vertebral fractures assessment. Analyses of efficacy were performed using an intention to treat approach to include all patients randomized to treatment who received at least one dose of study drug and underwent vertebral radiography at baseline and at least once during therapy. **External validity:** Silverman addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D.	Information was insufficient to allow judgment on allocation concealment. Withdrawals appeared high, with 33% of patients discontinuing the study. The proportions were unequal in terms of reason for discontinuation which may potentially affect internal validity. **External validity:** Bisphosphonate are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population. Patients from two of the four treatment arms received bazedoxifene, which is not marketed in Canada. This is not an appropriate comparator and as a result, these data were not extracted.