

**SUPPLEMENTARY APPENDIX 3: Evidence Report**

**2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis**

**Glucocorticoid Induced Osteoporosis (GIOP) – Evidence Report**

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## Introduction

This review focuses on glucocorticoid-induced osteoporosis (GIOP) among adults and children. It serves as an update to the 2017 ACR guideline on managing GIOP. The key questions addressed in this review are similar to those addressed in the previous review supporting the 2017 guideline, and where possible we combine relevant evidence from the previous review with newer evidence identified in the updated searches. In cases where we did not identify newer evidence, we pulled forward relevant evidence from the previous review. The update review includes additional PICO questions not addressed in the previous review. These questions focus on the use of sequential or combination therapies to treat GIOP (PICO 13.1 to 13.6).

Note that differences in the appearance of the evidence tables is due to differences in formats used in the previous review compared to the current review, which is formatted like more recent ACR guideline evidence reports. Preference in the current review is for the tables to include specific rows for the different GRADE domains (e.g., risk of bias, consistency, directness, and imprecision). Additionally, evidence summaries were not included in the previous review. Due to time constraints, we did not produce evidence summaries or re-evaluate certainty of evidence ratings for evidence pulled forward from the previous review. In cases where we merged evidence from the previous review with newer evidence identified in the updated searches, we did produce comprehensive evidence summaries and evidence tables. References for studies included in the previous review are listed at the end of this report. References to newer studies included in this updated review are listed directly beneath the evidence tables.

## Population of interest

The population of interest includes adults and children taking glucocorticoids (prednisone at  $\geq 2.5$  mg/day for  $>3$  months). The adult population was divided by age with questions specifically addressing men and women  $\geq 40$  years of age, with some questions specific to post-menopausal women, and questions addressing men and women (not of childbearing potential)  $<40$  years of age. Some questions consider risk of fracture, where risk is defined as:

- Low risk: Baseline 10-year fracture risk assessment by FRAX=  $<10\%$  for Major osteoporosis (OP) fracture and  $<2\%$  for hip fracture)
- Moderate risk: Baseline 10-year fracture risk assessment by FRAX=  $10\text{--}19\%$  for Major OP fracture and/or  $\geq 2$ , but  $<3\%$  for hip fracture)
- High Risk: Past fragility fracture, BMD T score  $\leq -2.5$  at the hip or spine, and/or baseline 10-year fracture risk assessment by FRAX  $\geq 20\%$  for Major OP fracture or  $\geq 3\%$  for hip fracture)

Special populations considered in the guideline include:

- Patients with organ transplants (and eGFR  $\geq 30$  and no evidence of metabolic bone disease),
- Patients receiving high-dose GCs (mean dose  $\geq 30$  mg daily for  $\geq 30$  days, and cumulative dose  $\geq 5$  gm over one year)
- Children (age 4 to 17 receiving GCs for  $>3$  months)

For the PICO questions on sequential or combination therapies (PICO 13.1 to 13.6), we included indirect evidence from studies focused on treating OP not related to glucocorticoid use.

### **Critical outcomes**

Each table reports the summary of findings from randomized trials and/or observational studies reporting the critical outcomes. The critical outcomes, as chosen by the Core Team, include:

- Fracture
- Bone mineral density (BMD, considered an indirect outcome)
- Treatment related adverse events (AEs), with atypical femoral fracture and osteonecrosis of the jaw considered the most important events to capture.

Note that serious adverse events are rare, and thus it is quite difficult to achieve a statistically significant difference between groups for this outcome in randomized trials powered for efficacy outcomes that occur much more often.

Not every study identified examined all critical outcomes. Each outcome was analyzed separately.

### **Interventions**

The following interventions were within the scope of this guideline:

- Calcium + vitamin D (CA/D, standard care); activated vitamin D
- Bisphosphonates (oral and infusion):
  - Alendronate (Fosamax), a weekly pill
  - Risedronate (Actonel), a weekly or monthly pill
  - Ibandronate (Boniva), a monthly pill or quarterly intravenous (IV) infusion
  - Zoledronic acid (Reclast), an annual IV infusion
- Selective Estrogen Receptor Modulator (SERM)
  - Raloxifene (Evista)
  - Bazedoxifene (what trade names?)
- Parathyroid hormone (PTH) /PTHrP analogs
  - Teriparatide (Forteo)
  - Abaloparatide (Tymlos)
- Anti-sclerostin monoclonal antibodies

- Romosozumab (Evenity)
- Receptor activator of NfκB-Ligand (RANKL) inhibitor
  - Denosumab (Prolia, Xgeva)
- Combinations (OP med + OP med + CA/D vs single OP med + CA/D)
  - PTH analog plus denosumab
  - Oral bisphosphonate plus PTH analog
  - IV bisphosphonate plus PTH analog
  - Oral bisphosphonate plus romosozumab
  - IV bisphosphonate plus romosozumab
  - Denosumab plus romosozumab
- Continue or switch OP med after decline in bone mineral density or sustained new fracture after 12 months of oral bisphosphonate
- Sequential therapy (varies depending on fracture risk, see PICO questions 13.1 to 13.6):
- Lifestyle: balanced diet, strengthening or weight-bearing exercise, smoking cessation, limited alcohol and caffeine intake; exercise only for children
- Fracture risk assessment or reassessment under following situations
  - Among patients who were either not recommended OP meds or recommended but not treated with them
  - To aid in decision to continue current OP treatment, stop treatment or change treatment (at least 1-year after starting OP med)
  - After completing a full course of OP medication

## **Systematic Literature Review**

For most of the PICO questions, randomized controlled trials (RCTs) were the source of evidence. However, for PICO questions (8.1 to 9.6) related to fracture risk assessment or re-assessment we included observational studies.

## **Certainty of Evidence Assessment**

Certainty of evidence assessment was performed separately for each outcome using the GRADE system, which results in one of four possible evidence grades that reflect level of confidence in the effect estimate: high, moderate, low, and very low. Study design is the starting point for quality assessment: randomized controlled trials (RCTs) start at high quality and observational studies start at low quality. Five factors can lower the quality of evidence grade: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Risk of bias refers to limitations in study design or execution (e.g., lack of allocation concealment or blinding). Inconsistency refers to unexplained heterogeneity in results of studies evaluating the same outcome. Indirectness refers to lack of direct comparisons of interventions of interest (e.g. studies comparing drug A vs. placebo and drug B vs. placebo when the comparison of interest is drug A vs. drug B), lack of applicability in the interventions or populations being evaluated, or use of indirect (surrogate) outcome measures. Imprecision refers to uncertainty in the estimate of effect due to very low

numbers of patients or events and/or wide 95% confidence intervals that cross a clinical decision threshold (i.e. between recommending and not recommending treatment). Publication bias refers to selective publication of studies that show greater treatment effects (i.e. negative studies are suppressed). Certainty of evidence can vary from outcome to outcome. The final certainty assessment for the PICO question is based on the critical outcome with the lowest quality assessment.

The level of evidence listed in this report for either an individual paper or a group of papers is not meant to be an absolute statement about the quality of the study (or studies) under consideration. Rather, the intention is to rate the paper(s) in relation to the question being asked in this guideline. Because of this, a very well conducted study might actually be rated down in this evidence report, possible reasons including that the population or intervention being studied does not completely match the population or intervention being examined by the PICO question in this guideline (in other words, downgrading for indirectness). The level of evidence may also be downgraded due to imprecision in the effect estimate (wide confidence intervals that cross the line of no effect, or a low number of patients or events). A combination of these factors may result in quality of evidence from a well-conducted study being rated as low.

### **Presentation of effects**

- The treatment effects from binary (yes or no) outcomes are presented as relative effects and absolute effects.
- Relative effects capture the difference between intervention and control in relative terms. For example, a 10% event rate in controls and a 5% event rate in the intervention represents a 50% relative risk reduction ( $10\% - 5\% / 10\%$ )
- The same difference represents a 5% absolute risk reduction ( $10\% - 5\% = 5\%$ ). In general, for patients, the absolute effect is the most important.
- Relative effects for dichotomous outcomes in the tables are expressed as relative risk (RR) or odds ratio (OR). RR is the default effect size because it is more easily interpretable, but under some circumstances, RRs can lead to impossible numbers when calculating absolute risk differences. In such instances, ORs were used instead of RRs.

### **Evidence Summaries including Summary of Findings (= Tables under each PICO question, except some PICO questions for which no evidence was available)**

- Direct comparisons are situations where trials directly compare drug A to drug B within one of the patient subgroups covered in this guideline.
- Indirect comparisons: Some studies do not include a direct comparison of drugs or interventions specified in a given PICO question. An example of this is trials that compare drug A to placebo, or an observational study where all patients received drug A and a pre-post comparison was made.

### **Interpreting the evidence**

It is important to take into account the information presented specifically as it relates to the question of interest. For example, when the only evidence for a given PICO question is indirect due to the comparison or patient population, the study is appropriately downgraded for indirectness as shown under the column labeled “indirectness.” If the 95% confidence interval around an effect size is wide and crosses the line of no difference between treatments, the evidence for that outcome is downgraded due to imprecision. Study design and risk of bias may result in downgrades in the certainty of evidence. The overall certainty of evidence considers all these factors, and is appropriately rated as high, moderate, low or very low. The certainty of evidence is key to your decisions.

### **Moving from evidence to recommendations**

- In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low certainty evidence almost invariably mandates a weak recommendation.
- There are, however, situations in which low certainty evidence can lead to strong recommendations. For instance, if there is low quality evidence favoring an intervention but high certainty evidence of important harm, then a strong recommendation against the intervention may be appropriate.

## I. MEN AND POST-MENOPAUSAL WOMEN OVER 40 TREATMENT QUESTIONS

### A: LOW RISK: BASELINE RISK ASSESSMENT BY FRAX <10% FOR MAJOR OP FRACTURE, <2% FOR HIP FRACTURE

#### 1.1.a. Vit D+Ca vs Placebo

In men and post-menopausal women ≥ age 40 who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium nor vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

Table 1. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR VITAMIN D+CA VS. PLA FOR ADULTS 40 YEARS AND OLDER

Bibliography: [Braun, et al. Clin Endocrinol \(Oxf\). 1983 Aug; 19\(2\): 265-73<sup>†</sup>; \[1\]](#) [Adachi, et al. J Rheumatol. 1996 Jun; 23\(6\): 995-1000 \[2\]](#)

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture	62 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3</sup>	Relative Risk 0.6 (0.16 to 2.3)	161 per 1000	65 fewer per 1000 (from 135 fewer to 210 more)
36 months	36 months	due to risk of bias, imprecision			
Vertebral Fracture	14 (1 RCT)	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>2,3,4,5</sup>	Relative Risk 3.0 (0.14 to 63.15)	0 per 1000	-
6 months	6 months	due to risk of bias, indirectness, imprecision			
Non-Vertebral Fracture	14 (1 RCT)	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>2,3,4,5</sup>	Relative Risk 0.33 (0.02 to 7.02)	143 per 1000	96 fewer per 1000 (from 140 fewer to 860 more)
6 months	6 months	due to risk of bias, indirectness, imprecision			
Serious Adverse Events					
			No data		

**Total Adverse Events**

No data

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients receiving Calcium and Vitamin D in the Braun, et al. study received 1 $\alpha$ -(OH) D3 (Etalpha), an active form of Vitamin D.

CI: Confidence interval; RR: Risk ratio

**Table 2. EVIDENCE FOR GENERAL OSTEOPOROSIS POPULATION VITAMIN D+CA VS. PLA FOR ADULTS 40 YEARS AND OLDER**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
<b>Hip Fracture</b>	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b>	<b>Relative Risk 0.98</b> (0.77 to 1.25)	<b>11 per 1000</b> Over a mean of 4.5 years	<b>0 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Vertebral Fracture</b>	42,115 (3 RCTs) 3 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b>	<b>Relative Risk 0.90</b> (0.74 to 1.09)	<b>10 per 1000</b> Over a mean of 5 years	<b>1 fewer per 1000</b> (from 3 fewer to 1 more)
<b>Non-Vertebral Fracture</b>	5,833 (2 RCTs) to 7 years	⊕⊕⊕⊖ <b>MODERATE</b>	<b>Relative Risk 0.93</b> (0.78 to 1.09)	<b>88 per 1000</b> Over a mean of 5 years	<b>6 fewer per 1000</b> (from 19 fewer to 8 more)

**Bibliography:** Crandall, et al. AHRQ CER 53, March 2012; Grant, et al., Lancet. 2005 May 7-13; 365 (9471):1621-8 <sup>[3]</sup>; Porthouse, et al. BMJ. 2005; 330(7498):1003 <sup>[4]</sup>; Jackson, et al. N Engl J Med. 2006;354(7):669-83 <sup>[5]</sup>; Salovaara, et al. J Bone Miner Res. 2010 Jul;25 (7):1487-95 <sup>[6]</sup>



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[Note: No explanation for downgrades were provided in the previous evidence review.](#)

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### **1.2.a Lifestyle vs CA/D**

In men and post-menopausal women  $\geq$  age 40 who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.3.a Lifestyle+CA/D vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications plus calcium, and vitamin D, versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.4.a Oral Bisphosphonate vs CA/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** Fourteen RCTs—two identified in the updated literature search (Fujieda et al. 2020, Shin et al. 2017) and twelve pulled forward from the previous review (Saadati et al. 2008, Li et al. 2010, Okada et al. 2008, Ozoran et al. 2007, Stoch et al. 2009, Yamada et al. 2007, Lems et al. 2006, Adachi et al 2001, Wallach et al. 2000, Tee et al. 2012, Hakala et al. 2012, Saag et al. 1998)—assessed the use of oral bisphosphonates, calcium, and vitamin D versus calcium and vitamin D alone in adult men and women (both pre-menopausal and post-menopausal) on chronic glucocorticoid treatment for various conditions.

Eight studies compared alendronate to calcium and vitamin D (Saadati et al 2008, Okada et al. 2008, Ozoran et al. 2007, Stoch et al. 2009, Lem et al. 2006, Adachi et al 2001, Tee et al. 2012, Saag et al. 1998), 3 compared risedronate to calcium and vitamin D (Fujieda et al. 2020, Yamada et al 2007, Wallach et al. 2000), and 3 studies compared ibandronate to calcium and vitamin D (Li et al. 2010, Hakala et al. 2012, Shin et al. 2017). Follow-up varied across studies, with 1 study assessing outcomes at 6-months, 11 studies at 12 months (Li et al. 2010, Okada et al. 2008, Ozoran et al. 2007, Stoch et al. 2009, Yamada et al. 2007, Lems et al. 2006, Wallach et al. 2000, Tee et al. 2012, Hakala et al. 2012, Saag et al. 1998, Shin

et al. 2017), 2 at 18 months (Saadati et al. 2008, Okada et al. 2008), and 1 at 24 months (Adachi et al. 2001). The outcomes reported included incidence of fractures (morphometric vertebral, clinical vertebral, non-vertebral, total, and hip), bone density (lumbar spine, femoral neck, total hip, and trochanter), any adverse event, serious adverse event, and gastrointestinal adverse events. Not all studies reported on each of these outcomes. The table below presents the findings for each outcome separately. Data from studies measuring outcomes at 18-months were combined with data from studies reporting outcomes at 12-months.

Uncertain to very uncertain evidence suggests that bisphosphonate treatment improves lumbar spine and femoral neck BMD at all follow-up times, but only improves hip BMD at 12 and 24-months follow-up. Similarly, uncertain to very uncertain evidence suggests that bisphosphonates may reduce total fractures and morphometric vertebral fractures (at 12 and 24 months follow-up). However, the differences are not statistically significant. There is no significant difference between bisphosphonates and placebo for other types of fractures (hip fracture or non-vertebral fracture). No statistically significant differences were observed between bisphosphonates and calcium/vitamin D alone for incidence of serious adverse events, total adverse events, or upper GI adverse events.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 3. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATES VS CALCIUM AND VITAMIN D ALONE**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
Incidence of morphometric vertebral fractures at 12 months												
7	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	22/629 (3.5%)	29/422 (6.9%)	Relative Risk 0.66 (0.25 to 1.77)	23 fewer per 1,000 (from 52 fewer to 53 more)	⊕⊕○○ Low	
Incidence of morphometric vertebral fractures at 24 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>d</sup>	none	1/143 (0.7%)	4/59 (6.8%)	<b>Relative Risk 0.10</b> (0.01 to 0.90)	<b>61 fewer per 1,000</b> (from 67 fewer to 7 fewer)	⊕⊕○○ Low	
<b>New clinical vertebral fractures at 12 months</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b,c</sup>	none	1/114 (0.9%)	0/59 (0.0%)	<b>Relative Risk 1.57</b> (0.06 to 37.84)	<b>0 fewer per 1,000</b> (from 0 fewer to 0 fewer)	⊕○○○ Very low	
<b>Incidence of non-vertebral fractures at 12 months</b>												
7	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	32/795 (4.0%)	24/558 (4.3%)	<b>Relative Risk 0.89</b> (0.52 to 1.53)	<b>5 fewer per 1,000</b> (from 21 fewer to 23 more)	⊕⊕○○ Low	
<b>Incidence of non-vertebral fractures at 24 months</b>												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	Serious <sup>a</sup>	not serious	not serious	very serious <sup>b,c</sup>	none	8/147 (5.4%)	6/61 (9.8%)	<b>Relative Risk 0.55</b> (0.20 to 1.53)	<b>44 fewer per 1,000</b> (from 79 fewer to 52 more)	⊕○○○ Very low	
<b>Hip fractures at 12 months</b>												
5	randomized trials	Serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	1/303 (0.3%)	2/229 (0.9%)	<b>Relative Risk 0.57</b> (0.09 to 3.56)	<b>4 fewer per 1,000</b> (from 8 fewer to 22 more)	⊕⊕○○ Low	
<b>Total Fractures at 6-months</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b,c</sup>	none	6/63 (9.5%)	4/34 (11.8%)	<b>Relative Risk 0.81</b> (0.25 to 2.67)	<b>22 fewer per 1,000</b> (from 88 fewer to 196 more)	⊕○○○ Very low	
<b>Total fractures at 12 months</b>												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
8	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	54/871 (6.2%)	49/631 (7.8%)	<b>Relative Risk 0.79</b> (0.49 to 1.27)	<b>16 fewer per 1,000</b> (from 40 fewer to 21 more)	⊕⊕○○ Low	
<b>Total fractures at 24 months</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	9/147 (6.1%)	10/61 (16.4%)	<b>Relative Risk 0.37</b> (0.16 to 0.87)	<b>103 fewer per 1,000</b> (from 138 fewer to 21 fewer)	⊕⊕○○ Low	
<b>Serious adverse events, incidence at 12 months</b>												
8	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b,c</sup>	none	132/718 (18.4%)	133/631 (21.1%)	<b>Relative Risk 0.89</b> (0.68 to 1.18)	<b>23 fewer per 1,000</b> (from 67 fewer to 38 more)	⊕⊕○○ Low	
<b>Serious adverse events, incidence at 24 months</b>												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b,c</sup>	none	9/55 (16.4%)	19/61 (31.1%)	<b>Relative Risk 0.53</b> (0.26 to 1.06)	<b>146 fewer per 1,000</b> (from 230 fewer to 19 more)	⊕○○○ Very low	
Total Adverse Events, incidence at 6 months												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b,c</sup>	none	19/63 (30.2%)	9/34 (26.5%)	<b>Relative Risk 1.14</b> (0.58 to 2.24)	<b>37 more per 1,000</b> (from 111 fewer to 328 more)	⊕○○○ Very low	
Total Adverse events, incidence at 24 months												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b,c</sup>	none	51/55 (92.7%)	55/61 (90.2%)	<b>Relative Risk 1.03</b> (0.92 to 1.15)	<b>27 more per 1,000</b> (from 72 fewer to 135 more)	⊕○○○ Very low	
Upper GI adverse events at 12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
5	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	139/620 (22.4%)	103/533 (19.3%)	<b>Relative Risk 1.18</b> (0.94 to 1.48)	<b>35 more per 1,000</b> (from 12 fewer to 93 more)	⊕⊕○○ Low	
Upper GI adverse events at 24 months												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b,c</sup>	none	17/55 (30.9%)	19/61 (31.1%)	<b>Relative Risk 0.99</b> (0.58 to 1.71)	<b>3 fewer per 1,000</b> (from 131 fewer to 221 more)	⊕○○○ Very low	
Total Hip BMD g/cm2 change at 6-months												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	serious <sup>b,c</sup>	none	63	34	-	Mean Difference <b>-1.71 lower</b> (-3.6 lower to 0.18 higher)	⊕○○○ Very low	
Total hip BMD g/cm2 change at 12 months												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
5	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	not serious	none	349	280	-	Mean Difference 1.5 higher (0.9 higher to 2.1 higher)	⊕⊕○○ Low	Favors BIS
Total Hip BMD g/cm2 change at 24 months												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	serious <sup>c</sup>	none	40	45	-	Mean Difference <b>4.26 higher</b> (2.32 higher to 6.2 higher)	⊕○○○ Very low	Favors BIS
Lumbar spine BMD g/cm2 change at 6 months												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	serious <sup>c</sup>	none	63	34	-	Mean Difference <b>3.37 higher</b> (0.76 higher to 5.98 higher)	⊕○○○ Very low	Favors BIS
Lumbar spine BMD g/cm2 change at 12 months												



Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
12	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	not serious	none	762	692	-	Mean Difference <b>4.73 higher</b> (2.78 higher to 6.68 higher)	⊕⊕○○ Low	Favors BIS
<b>Lumbar spine BMD g/cm2 change at 24 months</b>												
2	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	serious <sup>c</sup>	none	127	126	-	Mean Difference <b>5.2 higher</b> (4.02 higher to 6.37 higher)	⊕○○○ Very low	Favors BIS
<b>Femoral Neck BMD g/cm2 change at 6-months</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	serious <sup>c</sup>	none	63	34	-	Mean Difference <b>1.02 higher</b> (1.13 lower to 3.17 higher)	⊕○○○ Very low	Favors BIS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS plus CA and vit. D	CA and vit. D	Relative (95% CI)	Absolute (95% CI)		
Femoral neck BMD g/cm2 change at 12 months												
8	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	not serious	none	633	588	-	Mean Difference <b>2.55 higher</b> (1.53 higher to 3.58 higher)	⊕⊕○○ Low	Favors BIS
Femoral neck BMD g/cm2 change at 24 months												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	serious <sup>c</sup>	none	51	53	-	Mean Difference <b>3.54 higher</b> (1.05 higher to 6.03 higher)	⊕○○○ Very low	Favors BIS

CI: confidence interval; MD: mean difference; RR: risk ratio

a. High risk of bias, due mostly to attrition, unclear selection bias, and unclear blinding

b. Wide 95% confidence interval due to few events

c. Small sample size, <200 per treatment arm

d. Indirect outcome

**Newer Study References:**

Fujieda Y, Horita T, Nishimoto N, Tanimura K, Amasaki Y, Kasahara H, Furukawa S, Takeda T, Fukaya S, Matsui K, Tsutsumi A, Furusaki A, Sagawa A, Katayama K, Takeuchi K, Katsumata K, Kurita T, Shane P, Kato M, Oku K, Yasuda S, Takahata M, Iwasaki N, Atsumi T. Efficacy and safety of sodium RISedronate for glucocorticoid-induced Osteoporosis with rheumatoid arthritis (RISOTTO study): A multicentre, double-blind, randomized, placebo-controlled trial. *Mod Rheumatol*. 2021 May;31(3):593-599. doi: 10.1080/14397595.2020.1812835. Epub 2020 Oct 2. PMID: 32820698.

Shin K, Park SH, Park W, Baek HJ, Lee YJ, Kang SW, Choe JY, Yoo WH, Park YB, Song JS, Lee SG, Yoo B, Yoo DH, Song YW. Monthly Oral Ibandronate Reduces Bone Loss in Korean Women With Rheumatoid Arthritis and Osteopenia Receiving Long-term Glucocorticoids: A 48-week Double-blinded Randomized Placebo-controlled Investigator-initiated Trial. *Clin Ther*. 2017 Feb;39(2):268-278.e2. doi: 10.1016/j.clinthera.2017.01.008. Epub 2017 Feb 1. PMID: 28161119.

**TABLE 4. EVIDENCE AVAILABLE FOR BISPHOSPHONATES VS CALCIUM AND VITAMIN D ALONE IN GENERAL POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	21,811 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.71</b> (0.55 to 0.91)	<b>19 per 1000</b> Over a mean of 2.5 years	<b>6 fewer per 1000</b> (from 2 fewer to 8 fewer)
<b>Vertebral Fracture</b>	10,500 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.59</b> (0.51 to 0.68)	<b>88 per 1000</b> Over a mean of 2.5 years	<b>36 fewer per 1000</b> (from 28 fewer to 43 fewer)
<b>Non-Vertebral Fracture</b>	22,022 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.84</b> (0.77 to 0.91)	<b>106 per 1000</b> Over a mean of 2.5 years	<b>17 fewer per 1000</b> (from 10 fewer to 24 fewer)

**Bibliography:** Crandall, et al. *AHRQ CER* 53, March 2012; *Cochrane Database Syst Rev*. 2008 Jan 23; (1):CD001155. <sup>[21]</sup>; *Cochrane Database Syst Rev*. 2008 Jan 23; (1):CD004523 <sup>[22]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

### 1.5.a IV Bisphosphonate vs Ca/Vit D

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 5. EVIDENCE AVAILABLE FOR IV BISPHOSPHONATE VS CA/VIT D FOR GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b>	Relative Risk 0.70 (0.42 to 1.17)	23 per 1000 Over 3 years	7 fewer per 1000 (from 13 fewer to 4 more)
Vertebral Fracture	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b>	Relative Risk 0.57 (0.35 to 0.91)	109 per 1000 Over 3 years	47 fewer per 1000 (from 10 fewer to 71 fewer)
Non-Vertebral Fracture	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b>	Relative Risk 0.74 (0.56 to 0.94)	100 per 1000 Over 3 years	26 fewer per 1000 (from 6 fewer to 44 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#) <sup>[23]</sup>; [Lyles, et al., N Engl J Med. 2007; 357\(18\):1799-809](#) <sup>[24]</sup>.

Note: No explanation for downgrades were provided in the previous evidence review.

#### 11.6.a Selective Estrogen Receptor Modulators (SERM) vs Ca/Vit D

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The evidence base for this PICO question includes 2 RCTs—one identified in our updated searches (Cho et al., 2021) and the other pulled forward from the previous review (Mok et al., 2011). Both RCTs enrolled postmenopausal women (average age 57 years) who had been

taking low dose glucocorticoids ( $\leq 7.5$  mg) for at least 3 months for rheumatic diseases. Overall, these studies randomized 228 women to receive either bazedoxifene (20 mg/day, Cho, 2021) or raloxifene (60 mg/day, Mok, 2011) plus calcium (1000 to 1200 mg) and vitamin D (800 IU daily) or calcitriol (0.00025 mg/day) (n=114) or to placebo plus the same amount of calcium/vitamin D or calcitriol (n=114). Studies reported on lumbar spine (L-spine), hip, and femoral neck bone mineral density (BMD); new fractures; and adverse events. Follow-up in both studies was 12 months.

The overall risk of bias (ROB) for Cho was rated high due to lack of blinding of participants and clinicians and unclear blinding of outcomes assessors. ROB was low for Mok et al. 2011 as this study blinded all study staff and participants. Low certainty evidence from Mok et al. (2011) suggests significant increases in total hip and femoral neck BMD with raloxifene versus placebo. Low certainty of evidence suggests that treatment with either bazedoxifene or raloxifene significantly increases L-spine BMD (mean difference 0.01 higher, 95% CI: 0.01 higher to 0.02 higher). Fewer patients in the bazedoxifene or raloxifene group experienced new fractures compared to participants in the placebo group (1/108 [0.9%] versus 7/113 [6.2%], respectively). The difference, however, was not statistically significant. More patients in the bazedoxifene or raloxifene than placebo group reported experiencing non-serious adverse events (41/114 [36.0%] vs. 31/114 [27.2%], respectively). The difference was not statistically significant, with most participants reporting musculoskeletal events, gastrointestinal events, or infections. However, fewer participants in the bazedoxifene or raloxifene group reported serious adverse events (7/57 [12.3%] vs. 10/57 [17.5%], respectively, not a statistically significant difference). No deaths occurred in either study.

- **Certainty of evidence across all critical outcomes in GIOP population: Very Low**

**TABLE 6. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR SERM WITH CA/VITD VS CA/VITD ALONE**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral RAX or BAZ	PLA	Relative (95% CI)	Absolute (95% CI)		
Lumbar Spine BMD g/cm <sup>2</sup> at 12 months												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral RAX or BAZ	PLA	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	108	113	-	Mean Difference <b>0.01 higher</b> (0.01 higher to 0.02 higher)	⊕○○○ Very Low	Favors Oral RAX or BAZ
<b>Total hip BMD g/cm<sup>2</sup> at 12 months</b>												
1	randomized trials	Not serious	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	51	56	-	Mean Difference <b>1.8 higher</b> (0.86 higher to 2.74 higher)	⊕⊕○○ Low	Favors Oral RAX
<b>Femoral neck BMD g/cm<sup>2</sup> at 12 months</b>												
1	randomized trials	not serious	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	51	56	-	Mean Difference <b>0.15 lower</b> (1.5 lower to 1.2 higher)	⊕⊕○○ Low	Favors Oral RAX
<b>New vertebral fractures at 12 months</b>												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral RAX or BAZ	PLA	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>d</sup>	none	1/108 (0.9%)	7/113 (6.2%)	<b>Relative Risk 0.21</b> (0.04 to 1.21)	<b>49 fewer per 1,000</b> (from 59 fewer to 13 more)	⊕⊕○○ Low	
<b>Total AE at 12 months</b>												
2	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>d</sup>	none	41/114 (36.0%)	31/114 (27.2%)	<b>Relative Risk 1.28</b> (0.63 to 2.60)	<b>76 more per 1,000</b> (from 101 fewer to 435 more)	⊕⊕○○ Low	
<b>Serious Adverse Events</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>d</sup>	none	7/57 (12.3%)	10/57 (17.5%)	<b>Relative Risk 0.70</b> (0.29 to 1.71)	<b>53 fewer per 1,000</b> (from 125 fewer to 125 more)	⊕⊕○○ Low	

a. Lack of blinding of participants and clinicians and unclear blinding of outcome assessors

b. Indirect outcome

c. Small overall sample size

d. Wide 95% confidence intervals

#### References:

Cho, S. K., Kim, H., Lee, J., Nam, E., Lee, S., Choi, Y. Y., & Sung, Y. K. (2021, Jul 2). Effectiveness of bazedoxifene in preventing glucocorticoid-induced bone loss in rheumatoid arthritis patients. *Arthritis Res Ther*, 23(1), 176. <https://doi.org/10.1186/s13075-021-02564-1>

Mok CC, Ying KY, To CH, Ho LY, Yu KL, Lee HK, Ma KM.. Raloxifene for prevention of glucocorticoid-induced bone loss: a 12-month randomised double-blinded placebo-controlled trial. Annals of the Rheumatic Diseases 2011;70(5):778-84. [Other: ; PubMed: 21187295]

**TABLE 7. EVIDENCE FOR SERM VS. CA/VITAMIN D IN GENERAL POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Raloxifene (95% CI)**
<b>Hip Fracture</b>	10,101 (1 RCT) 5.6 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk</b> <b>0.86</b> (0.65 to 1.15)	<b>7 per 1000</b> Over 3 years	<b>1 fewer per 1000</b> (from 2 fewer to 1 more)
<b>Vertebral Fracture</b>	5,600 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk</b> <b>0.60</b> (0.49 to 0.74)	<b>101 per 1000</b> Over 3 years	<b>40 fewer per 1000</b> (from 26 fewer to 52 fewer)
<b>Non-Vertebral Fracture</b>	13,835 (2 RCTs) 3 to 5.6 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk</b> <b>0.80</b> (0.51 to 1.25)	<b>93 per 1000</b> Over 3 years	<b>19 fewer per 1000</b> (from 46 fewer to 23 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#) <sup>[23]</sup>; [Ensrud, et al. J Bone Miner Res. 2008;23 \(1\):112-20](#) <sup>[26]</sup>; [Seeman, et al. Osteoporos Int. 2006;17\(2\):313-6](#) <sup>[27]</sup>; [Silverman, et al. J Bone Miner Res. 2008;23 \(12\):1923-34](#) <sup>[28]</sup>.

### 1.7a Teriparatide vs Ca/Vit D

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 8. EVIDENCE AVAILABLE FOR TERIPARATIDE VS CA/VIT D IN GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
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Follow up				Risk with Calcium and Vitamin D alone*	Risk difference with Teriparatide (95% CI)**
<b>Hip Fracture</b>	1,637 (1 RCT) 2 years	⊕⊕⊖⊖ <sup>1,2</sup> <b>LOW</b>	<b>Relative Risk 0.50</b> (0.09 to 2.73)	<b>7 per 1000</b> Over 2 years	<b>4 fewer per 1000</b> (from 6 fewer to 12 more)
<b>Vertebral Fracture</b>	4,359 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.36</b> (0.28 to 0.47)	<b>143 per 1000</b> Over 2 years	<b>92 fewer per 1000</b> (from 76 fewer to 103 fewer)
<b>Non-Vertebral Fracture</b>	2,377 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.62</b> (0.48 to 0.82)	<b>97 per 1000</b> Over 2 years	<b>37 fewer per 1000</b> (from 18 fewer to 50 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#) <sup>[23]</sup>; [Neer, et al., N Engl J Med. 2001 May 10; 344\(19\):1434-41](#) <sup>[29]</sup>; [Stevenson, et al. Health Technol Assess. 2005 Jun;9\(22\):1-160](#) <sup>[30]</sup>; [Vestergaard, et al. Osteoporos Int. 2007 Jan;18\(1\):45-57](#) <sup>[31]</sup>

<sup>1</sup> Noted uneven distribution of discontinuations; very low discontinuation rate overall.

<sup>2</sup> 95% CI is wide

### 1.8.a Abaloparatide vs Ca/Vit D

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 1.9.a Denosumab vs Ca/Vit D

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

TABLE 9. EVIDENCE AVAILABLE FOR DENOSUMAB VS CA/VIT D IN GENERAL OSTEOPOROSIS POPULATION:

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Denosumab (95% CI)**
Hip Fracture	7,297 (1 RCT) 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	Relative Risk 0.59 (0.36 to 0.94)	11 per 1000 Over 3 years	5 fewer per 1000 (from 1 fewer to 7 fewer)
Vertebral Fracture	7,738 (2 RCTs) 2 to 3 years	⊕⊕⊕⊕ <b>HIGH</b>	Relative Risk 0.32 (0.25 to 0.41)	72 per 1000 Over 3 years	49 fewer per 1000 (from 43 fewer to 54 fewer)
Non-Vertebral Fracture	7,657 (2 RCTs) 2 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>2</sup> due to imprecision	Relative Risk 0.65 (0.28 to 1.51)	75 per 1000 Over 3 years	26 fewer per 1000 (from 54 fewer to 38 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#); <sup>[23]</sup> [Bone, et al. J Clin Endocrinol Metab. 2008; 93 \(6\):2149-57](#) <sup>[32]</sup>; [Cummings, et al. N Engl J Med. 2009 Aug 20; 361 \(8\):756-65](#) <sup>[33]</sup>

<sup>1</sup> Outcome is only assessed by one study

<sup>2</sup> 95% CI of one trial passes beyond the other and passes null effect

#### 1.10.a Anti-sclerostin (Romosozumab) vs Ca/Vit D

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 1.11.a IV bisphosphonates vs Oral bisphosphonate

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D, versus treatment with oral bisphosphonate, calcium, and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 10. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR IV BISPHOSPHONATES VS ORAL BISPHOSPHONATE**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture	833 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3</sup> due to imprecision	<b>Relative Risk 1.67</b> (0.4 to 6.95)	<b>7 per 1000</b>	<b>5 more per 1000</b> (from 4 fewer to 43 more)
12 months					
Non-Vertebral Fracture					
			No data		
Serious Adverse Events	833 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,3</sup> due to imprecision	<b>Relative Risk 0.99</b> (0.74 to 1.32)	<b>185 per 1000</b>	<b>2 fewer per 1000</b> (from 48 fewer to 59 more)
Total Adverse Events	833 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,3</sup> due to imprecision	<b>Relative Risk 1.16</b> (1.06 to 1.26)	<b>669 per 1000</b>	<b>107 more per 1000</b> (from 40 more to 174 more)

**Bibliography:** [Reid, et al. Lancet. 2009 Apr 11; 373\(9671\): 1253-63](#) <sup>[34]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

<sup>3</sup> Per Panel Request, Reid 2009 was downgraded from an original grade of “Moderate” to a new grade of “Low” (5/14/16)

**TABLE 11. EVIDENCE AVAILABLE FOR IV BISPHOSPHONATES VS ORAL BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants	Certainty of the evidence	Relative effect	Anticipated absolute effects
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(studies) Follow up		(GRADE)	(95% CI)	Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
<b>Hip Fracture</b>			No data		
<b>Vertebral Fracture</b>	131 (2 RCTs) 1 year	⊕⊕⊕⊕ <sup>1,2,3</sup> <b>VERY LOW</b>	<b>Relative Risk 1.50</b> (0.29 to 7.73)	<b>31 per 1000</b> Over 1 year	<b>15 more per 1000</b> (from 22 fewer to 207 more)
<b>Non-Vertebral Fracture</b>			No data		
<b>Bibliography:</b> Crandall, et al. AHRQ CER 53, March 2012; Tauchmanová, et al. Bone Marrow Transplant. 2006 Jan; 37 (1):81-8 <sup>[35]</sup> ; Chávez-Valencia, et al. J Clin Densitom. 2014 Oct-Dec;17(4):484-9 <sup>[36]</sup>					

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

<sup>3</sup> Per Panel Request, Reid 2009 was downgraded from an original grade of “Moderate” to a new grade of “Low” (5/14/16)

### 1.12. a SERM vs Oral bisphosphonate

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, vitamin D, versus treatment with oral bisphosphonate calcium, vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

TABLE 12. EVIDENCE AVAILABLE FOR SERM VS ORAL BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Raloxifene (95% CI)**

<b>Hip Fracture</b>	1,412 (1 RCT) 2 years	⊕⊕⊕⊕ <sup>1,2</sup> <b>LOW</b>	<b>Relative Risk 2.04</b> (0.19 to 22.45)	<b>1 per 1000</b> Over 2 years	<b>1 more per 1000</b> (from 1 fewer to 30 more)
<b>Vertebral Fracture</b>	514 (1 RCT) 2 years	⊕⊕⊕⊕ <sup>1,2</sup> <b>LOW</b>	<b>Relative Risk 0.62</b> (0.20 to 1.86)	<b>31 per 1000</b> Over 2 years	<b>12 fewer per 1000</b> (from 25 fewer to 27 more)
<b>Non-Vertebral Fracture</b>	1,412 (1 RCT) 2 years	⊕⊕⊕⊕ <sup>1,2</sup> <b>LOW</b>	<b>Relative Risk 1.09</b> (0.53 to 2.25)	<b>20 per 1000</b> Over 2 years	<b>2 more per 1000</b> (from 9 fewer to 25 more)

**Bibliography:** [Recker, et al. Bone. 2007 Apr;40\(4\):843-51](#) <sup>[37]</sup>

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

### 1.13.a Teriparatide vs Oral Bisphosphonate

In men and post-menopausal women ≥ age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** Two RCTs addressed this PICO-one identified in the updated searchers (Tanka, et al. 2020, TOWER-GO study) and one pulled forward from the previous review (Saag et al. 2007, 2009). Tanka et al (2020) randomized 180 adult men and women with a mean age of 66 years receiving low (≥5 mg/day) to high dose (≥20 mg/day) prednisone for > 3 months to weekly subcutaneous injections of teriparatide (56.5 µg, n=89) or to oral alendronate (35mg, n=35). All patients received calcium 610 mg and vitamin D 400 IU. In the other RCT, Saag et al. (2007, 2009) randomized 428 adult men and women (both post and pre-menopausal) with an average age of 61 years taking glucocorticoids ≥5 mg/day for ≥3months to daily subcutaneous injections of teriparatide (20 µg, n=214) or to oral alendronate (10 mg/day, n=214) plus subcutaneously injected placebo. All patients received supplements of calcium (1,000 mg/day) and vitamin D (800 IU/day). Outcomes reported included changes in lumbar spine bone mineral density (BMD), fracture incidence, and adverse effects at 18 and 36 months follow-up.

Risk of bias for both studies was rated high for attrition (>25%) and unclear for randomization process and allocation concealment. Low to very low certainty of evidence found no significant differences between groups in any type of fracture or in lumbar-spine BMD. Low certainty of evidence suggests that teriparatide may be associated with more participants experiencing adverse events. Differences, however, were small and not statistically significant. No difference was seen between groups in incidence of gastrointestinal adverse events.

- **Certainty of evidence across all critical outcomes for GIOP population: Very Low**

TABLE 13. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR TERIPARATIDE VS ORAL BISPSPHONATE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriparatide	Bisphosphonates	Relative (95% CI)	Absolute (95% CI)		
Incidence of Vertebral Fracture (18 mo)												
2	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	6/229 (2.6%)	14/244 (5.7%)	Relative Risk 0.45 (0.02 to 8.67)	32 fewer per 1,000 (from 56 fewer to 440 more)	⊕⊕○○ Low	
Incidence of Vertebral Fracture (36 mo)												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b,c</sup>	none	3/173 (1.7%)	13/169 (7.7%)	Relative Risk 0.23 (0.07 to 0.78)	59 fewer per 1,000 (from 72 fewer to 17 fewer)	⊕⊕○○ Low	
Incidence of Non-Vertebral Fragility Fracture (18 mo)												
2	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	12/272 (4.4%)	9/293 (3.1%)	Relative Risk 1.38 (0.59 to 3.20)	12 more per 1,000 (from 13 fewer to 68 more)	⊕⊕○○ Low	
Incidence of Non-Vertebral Fragility Fracture (36 mo)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriparatide	Bisphosphonates	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	16/214 (7.5%)	15/214 (7.0%)	<b>Relative Risk 1.07</b> (0.54 to 2.10)	<b>5 more per 1,000</b> (from 32 fewer to 77 more)	⊕⊕○○ Low	
<b>Incidence of SAEs (18 mo)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	45/214 (21.0%)	39/214 (18.2%)	<b>Relative Risk 1.15</b> (0.79 to 1.70)	<b>27 more per 1,000</b> (from 38 fewer to 128 more)	⊕⊕○○ Low	
<b>Incidence of SAEs (36 mo)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	70/214 (32.7%)	64/214 (29.9%)	<b>Relative Risk 1.09</b> (0.83 to 1.45)	<b>27 more per 1,000</b> (from 51 fewer to 135 more)	⊕⊕○○ Low	
<b>Total AEs (18 mo)</b>												
2	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	229/295 (77.6%)	213/304 (70.1%)	<b>Relative Risk 1.08</b> (0.99 to 1.18)	<b>56 more per 1,000</b> (from 7 fewer to 126 more)	⊕⊕○○ Low	
<b>Total AEs (36 mo)</b>												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriparatide	Bisphosphonates	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	194/214 (90.7%)	184/214 (86.0%)	<b>Relative Risk 1.05</b> (0.98 to 1.13)	<b>43 more per 1,000</b> (from 17 fewer to 112 more)	⊕⊕○○ Low	
<b>GI adverse events, incidence (18 mo)</b>												
2	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	106/295 (35.9%)	113/304 (37.2%)	<b>Relative Risk 0.84</b> (0.40 to 1.75)	<b>59 fewer per 1,000</b> (from 223 fewer to 279 more)	⊕⊕○○ Low	
<b>Lumbar-spine BMD g/cm<sup>2</sup></b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	serious <sup>b,c</sup>	none	58	79	-	Mean Difference <b>0.51 lower</b> (-2.34 lower to 1.32 higher)	⊕○○○ Very low	

CI: confidence interval; MD: mean difference; RR: risk ratio

a. Unclear reporting of randomization process and high attrition >25%

b. Wide 95% confidence intervals

c. Small sample size

d. Indirect outcome

## References



Tanaka I, Tanaka Y, Soen S, Oshima H. Efficacy of once-weekly teriparatide in patients with glucocorticoid-induced osteoporosis: the TOWER-GO study. J Bone Miner Metab. 2021 May;39(3):446-455. doi: 10.1007/s00774-020-01171-5. Epub 2020 Nov 19. PMID: 33211212.

Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357(20):2028-2039.

Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009;60(11):3346-3355.

**TABLE 14. EVIDENCE AVAILABLE FOR TERIPARATIDE IN GENERAL OSTEOPOROSIS POPULATION**

**Evidence Available for General Osteoporosis Population:**

Evidence Available for General Osteoporosis Population:					
Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture					
			No data		
Non-Vertebral Fracture	146 (1 RCT) 1 year	⊕⊕⊖⊖ <sup>1,2</sup> LOW	Relative Risk 0.30 (0.09 to 1.05)	137 per 1000 1 year	Over 96 fewer per 1000 (from 125 fewer to 7 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Body, et al. J Clin Endocrinol Metab. 2002 Oct;87\(10\):4528-35](#) <sup>[40]</sup>

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

#### 1.14.a Abaloparatide vs Oral bisphosphonate

In men and post-menopausal women ≥ age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 1.15.a,b,c Denosumab vs Oral bisphosphonate

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

**Summary:** The literature search identified one randomized controlled trial (RCT) that compared denosumab to an oral bisphosphonate. Saag et al (2019, 2018) randomized 795 adults >18 years who had been receiving >7.5 mg daily prednisone or equivalent for either <3 months (GC-initiating) or >3 months (GC continuing) to denosumab (60 mg subcutaneously Q6M, n=145 GC initiating and n=253 GC continuing) or risedronate (5 mg, n=145 GC initiating and n=252 GC continuing). All patients received daily supplementation with calcium ( $\geq$ 1,000 mg) and vitamin D ( $\geq$ 800 IU). Patients <50 years in this study were required to have a history of osteoporosis-related fracture. Patients  $\geq$ 50 years in the GC-continuing subpopulation were required to have a lumbar spine, total hip, or femoral neck BMD T score of  $-2.0$  or less, or a T score of  $-1.0$  or less with a history of osteoporosis-related fracture. Women of childbearing age were required to be on two forms of contraception. Follow-up in this study was 24-months.

Outcomes reported included lumbar spine (LS), total hip, and femoral neck bone mineral density (BMD) scores, fractures, and adverse events. Low certainty of evidence suggests that denosumab is superior to risedronate in increasing BMD in lumbar spine and total hip at 24 months (lumbar spine, glucocorticoid initiating, 6.2% v 1.7%). Adverse events such as death, serious infections, or fractures were similar between groups. Weaknesses of the study include a high attrition rate around 25% that was similar between both denosumab and risedronate groups. The study also did not utilize intention-to-treat analysis.

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 15. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR DENOSUMAB VS RISENDRONATE**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEN	RIS	Relative (95% CI)	Absolute (95% CI)		
Lumbar Spine BMD Change 24 months--Overall												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	290	287	-	Mean Difference <b>3.82 higher</b> (2.55 higher to 5.1 higher)	⊕⊕○○ Low	Favors Denosumab

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEN	RIS	Relative (95% CI)	Absolute (95% CI)		
Lumbar Spine BMD g/cm² Change 24 months - GC-initiating												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	107	113	-	Mean Difference <b>4.5 higher</b> (3.2 higher to 5.8 higher)	⊕⊕○○ Low	Favors Denosumab
Lumbar Spine BMD g/cm² Change 24 months - GC-continuing												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	183	174	-	Mean Difference <b>3.2 higher</b> (2 higher to 4.4 higher)	⊕⊕○○ Low	Favors Denosumab
Total Hip BMD g/cm² Change 24 months--Overall												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	285	287	-	Mean Difference <b>2.69 higher</b> (2.01 higher to 3.37 higher)	⊕⊕○○ Low	Favors Denosumab
Total Hip BMD g/cm² Change 24 months - GC-initiating												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEN	RIS	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	104	111	-	Mean Difference <b>3.1 higher</b> (2.2 higher to 4 higher)	⊕⊕○○ Low	Favors Denosumab
<b>Total Hip BMD g/cm<sup>2</sup> Change 24 months - GC-continuing</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	181	176	-	Mean Difference <b>2.4 higher</b> (1.7 higher to 3.1 higher)	⊕⊕○○ Low	Favors Denosumab
<b>Femoral Neck BMD g/cm<sup>2</sup> Change 24 months</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	285	287	-	Mean Difference <b>2.1 higher</b> (1.32 higher to 2.88 higher)	⊕⊕○○ Low	Favors Denosumab
<b>Femoral Neck BMD g/cm<sup>2</sup> Change 24 months - GC-initiating</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	104	111	-	Mean Difference <b>2.4 higher</b> (1.3 higher to 3.5 higher)	⊕⊕○○ Low	Favors Denosumab

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEN	RIS	Relative (95% CI)	Absolute (95% CI)		
Femoral Neck BMD g/cm² Change 24 months - GC-continuing												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	181	176	-	Mean Difference <b>1.8 higher</b> (0.7 higher to 2.9 higher)	⊕○○○ Very low	Favors Denosumab
Fracture through 24 months												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	71/1134 (6.3%)	75/1140 (6.6%)	<b>Relative Risk 0.95</b> (0.64 to 1.41)	<b>3 fewer per 1,000</b> (from 24 fewer to 27 more)	⊕⊕○○ Low	
Fracture through 24 months - Any osteoporosis-related fracture												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	35/398 (8.8%)	36/397 (9.1%)	<b>Relative Risk 0.97</b> (0.62 to 1.51)	<b>3 fewer per 1,000</b> (from 34 fewer to 46 more)	⊕⊕○○ Low	
Fracture through 24 months - New and worsening vertebral fracture												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	15/338 (4.4%)	24/346 (6.9%)	<b>Relative Risk 0.64</b> (0.34 to 1.20)	<b>25 fewer per 1,000</b> (from 46 fewer to 14 more)	⊕⊕○○ Low	
Fracture through 24 months - Non-vertebral fracture (low trauma)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEN	RIS	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	21/398 (5.3%)	15/397 (3.8%)	Relative Risk 1.40 (0.73 to 2.67)	15 more per 1,000 (from 10 fewer to 63 more)	⊕⊕○○ Low	
<b>Death</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	13/394 (3.3%)	9/385 (2.3%)	Relative Risk 1.41 (0.61 to 3.26)	10 more per 1,000 (from 9 fewer to 53 more)	⊕⊕○○ Low	
<b>Atypical Femoral Fracture</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	1/394 (0.3%)	0/385 (0.0%)	Relative Risk 2.93 (0.12 to 71.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	
<b>Osteonecrosis of the Jaw</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	not serious	none	0/394 (0.0%)	0/385 (0.0%)	not estimable		⊕⊕⊕○ Moderate	
<b>Malignancy</b>												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	12/394 (3.0%)	7/385 (1.8%)	Relative Risk 1.68 (0.67 to 4.21)	12 more per 1,000 (from 6 fewer to 58 more)	⊕⊕○○ Low	
<b>Any Serious Infection</b>												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEN	RIS	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	23/394 (5.8%)	25/385 (6.5%)	Relative Risk 0.90 (0.52 to 1.56)	6 fewer per 1,000 (from 31 fewer to 36 more)	⊕⊕○○ Low	

CI: confidence interval; MD: mean difference; RR: risk ratio

a. no ITT. 20% attrition.

b. indirect outcome

c. CI crosses line of no difference.

## References

\*Saag, K. G., Pannacciulli, N., Geusens, P., Adachi, J. D., Messina, O. D., Morales-Torres, J., Emkey, R., Butler, P. W., Yin, X., & Lems, W. F. (2019). Denosumab Versus Risedronate in Glucocorticoid-Induced Osteoporosis: Final Results of a Twenty-Four-Month Randomized, Double-Blind, Double-Dummy Trial. *Arthritis & rheumatology (Hoboken, N.J.)*, 71(7), 1174–1184. <https://doi.org/10.1002/art.40874>

\*Saag KG, Wagman RB, Geusens P, Adachi JD, Messina OD, Emkey R, Chapurlat R, Wang A, Pannacciulli N, Lems WF. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol.* 2018 Jun;6(6):445-454. doi: 10.1016/S2213-8587(18)30075-5. Epub 2018 Apr 6. PMID: 29631782.

\*Same patient population; tables only include data from more recent publication (2019).

### 1.16.a Romosumab vs Oral bisphosphonate

In men and post-menopausal women ≥ age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 1.17.a. SERM vs IV bisphosphonate

In post-menopausal women ≥ age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, vitamin D, versus treatment with IV bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.18.a Teriparatide vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.19.a Abaloparatide vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.20.a Denosumab vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.21.a Romosozumab vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**



#### 1.22.a Teriparatide vs SERM

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 1.23.a Abaloparatide vs SERM

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 1.24.a Denosumab vs SERM

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 1.25.a Romosozumab vs SERM

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 1.26.a Denosumab vs Teriparatide

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with teriparatide, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 1.27.a Denosumab vs Abalaparotide

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with abalaparotide, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 1.28.a Denosumab vs Romosozumab

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with romosozumab, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## **B: MODERATE RISK: RISK ASSESSMENT BY FRAX 10-19% FOR MAJOR OP FRACTURE, >2% FOR HIP FRACTURE**

### 1.1.b. Vit D+Ca vs Placebo

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

**Summary:** See Evidence Summary under Low Risk

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

### 1.2.b. lifestyle vs Ca/D

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 1.3.b. lifestyle+Ca/D vs Ca/Vit D

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium, vitamin D, and lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.4.b. Oral bisphosphonate vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** See Evidence Summary under Low Risk

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.5.b. IV bisphosphonate vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.6.b. SERM vs Ca/Vit D**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** See Evidence Summary under Low Risk

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.7.b. Teriparatide vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.8b Abaloparatide vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.9.b. Denosumab vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.10.b Romosozumab vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.11.b. IV bis vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D, versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** See Evidence Summary under Low Risk

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

### **1.12.b. SERM vs Oral bisphosphonate**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D (women)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.13.b. Teriparatide vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

**Summary:** See Evidence Summary under Low Risk.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.14ba Abaloparatide vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.15.b. Denosumab vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

See Evidence Summary under Low Risk

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

#### **1.16b Romosozumab vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.17.b.SERM vs IV bisphosphonate**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, vitamin D, versus treatment with IV bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.18.b Teriparatide vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.19.b Abaloparatide vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.20.b Denosumab vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.21.b Romosozumab vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.22.b. Teriparatide vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.23.b Abaloparatide vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.24.b. Denosumab vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.25.b Romosozumab vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with raloxifene calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.26.b. Denosumab vs Teriparatide**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with teriparatide, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.27.b Denosumab vs Abaloparatide**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with abaloparatide, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.28.b Denosumab vs Romosozumab**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with romosozumab, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**C: HIGH RISK: PAST FRAGILITY FRACTURE, BMD T SCORE  $\leq$  -2.5 AT THE HIP OR SPINE, AND/OR BASELINE RISK ASSESSMENT BY FRAX  $\geq$  20% FOR MAJOR OP FRACTURE,  $\geq$ 3% FOR HIP FRACTURE)**

#### **1.1.c. Vit D+Ca vs Placebo**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.2.c. lifestyle vs CA/D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** See Evidence Summary under Low Risk.



- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.3.c. lifestyle+CA/D vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium, vitamin D, and lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.4.c. Oral bisphosphonate vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** See Evidence Summary under Low Risk

**Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.5.c. IV bisphosphonate vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.6.c. SERM vs Ca/Vit D**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with SERM, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.7.c. Teriparatide vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.8.c Abaloparatide vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.9.c Denosumab vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.10.c Romosozumab vs Ca/Vit D**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D, versus treatment with calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.11.c. IV bisphosphonate vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D, versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** See Evidence Summary under Low Risk

**Certainty of evidence across all critical outcomes for GIOP population: Low**

**1.12.c. SERM vs Oral bisphosphonate**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with SERM, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D (women)?

**Summary:** See Evidence Summary under Low Risk

**Certainty of evidence across all critical outcomes for GIOP population: Very low**

**1.13.c. Teriparatide vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

**Summary:** See Evidence Summary under Low Risk

**Certainty of evidence across all critical outcomes for GIOP population: Very low**

**1.14.c. Abaloparatide vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**1.15.c. Denosumab vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

See Evidence Summary under Low Risk

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**1.16.c. Romosozumab vs Oral bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, vitamin D, versus treatment with oral bisphosphonate, calcium, vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.17.c. SERM vs IV bisphosphonate**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with SERM, calcium, vitamin D, versus treatment with IV bisphosphonate, calcium, vitamin D (women)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.18.c. Teriparatide vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.19.c. Abaloparatide vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.20.c. Denosumab vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.21.c Romosozumab vs IV bisphosphonate**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D, versus treatment with IV bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.22.c. Teriparatide vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D, versus treatment with SERM, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.23.b Abaloparatide vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D, versus treatment with SERM, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.24.c. Denosumab vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with SERM, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.25.c Romosozumab vs SERM**

In post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with SERM, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.26.c. Denosumab vs Teriparatide**

In men and post-menopausal women  $\geq$  age 40 and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with teriparatide, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.27.c Denosumab vs Abaloparatide**

In men and post-menopausal women  $\geq$  age 40 and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with abaloparatide, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **1.28.c Denosumab vs Romosozumab**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D, versus treatment with romosozumab, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## ***II. COMBINATION THERAPY TREATMENT QUESTIONS***

#### **1.29 What are the benefits or harms of using oral bisphosphonate plus denosumab?**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate plus denosumab, calcium, and vitamin D, versus treatment with one agent alone, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 1.30 What are the benefits or harms of using IV bisphosphonate plus denosumab?

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate plus denosumab, calcium, and vitamin D, versus treatment with one agent alone, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 1.31. What are the benefits or harms of using PTH analog plus denosumab?

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with PTH analog plus denosumab, calcium, and vitamin D, versus treatment with one agent alone, calcium, and vitamin D?

**Summary:** The literature searches identified three trials reporting on the findings of the DATA study. The first study, the original DATA study, randomized 94 post-menopausal women to receive denosumab (60mg SC every 6 month, n=33), teriparatide (20 mcg SC daily, n=31), or combined teriparatide and denosumab (n=30) (Tsai, et al. 2013). In this study, women were followed for 12 months. The second study, the DATA Extension study, followed women who completed the 12-month study period of the DATA trial for an additional 12 months (Leder et al. 2014). At the end of the extension study, women who completed the 24-month DATA trial time period were enrolled into the DATA-SWITCH trial. In this trial, women who were originally given teriparatide were switched to denosumab (n=27), women given denosumab were switched to teriparatide (n=27), and women given combination therapy were switched to denosumab (n=23). Women in this trial were followed for 24 months.

The women in these trials were 45 years or older (mean age 66 years) and were considered to be at high risk for fracture. High fracture risk was defined according to the following criteria: T score  $-2.5$  or less at the spine, hip, or femoral neck; T score  $-2.0$  or less with at least one BMD-independent risk factor (fracture after age 50 years, parental hip fracture after age 50 years, previous hyper-thyroidism, inability to get up from a chair with arms raised, or current smoking); or T score  $-1.0$  or less with history of fragility fracture. Women who had taken glucocorticoids or oral bisphosphonates within 6 months before enrolment, oestrogen, selective oestrogen-receptor modulators, or calcitonin within 3 months before enrollment, or who had ever received intravenous bisphosphonates, teriparatide, PTH, or strontium ranelate were excluded.

The risk of bias for the DATA trials was rated high due to unclear allocation concealment and high for selective outcome reporting. The DATA studies did not report on fracture outcomes despite choosing a study a population defined by their fracture risk; thus, raising concern for reporting bias. Very low certainty of evidence suggests that at 12 months, BMD was higher at all measured sites in the combination group

compared to the teriparatide only group (lumbar spine = 2.9%, femoral neck = 3.4%, and total hip = 4.2%,) and the denosumab only group (lumbar spine = 2.1%, femoral neck = 3.5%, and total hip = 2.4%,). Similarly, at 24 months, BMD was higher in the combination group compared to teriparatide alone (lumbar spine=3.4%, femoral neck=4.0%, and total hip=4.3%) and denosumab alone (lumbar spine=3.6%, femoral neck=3.6%, and total hip=3.1%). Authors of the studies reported that adverse events were balanced across treatment groups. Because the DATA-SWITHCH trial did not re-randomize women to transition to denosumab, we did not conduct a quantitative analysis to calculate between group effect estimates. Instead, we present the findings for each group in Table17. Narrative synthesis suggests that BMD at the lumbar spine improved more in the teriparatide monotherapy-to-denosumab monotherapy arm relative to combination (teriparatide+denosumab)-to-denosumab monotherapy and denosumab monotherapy-to-teriparatide monotherapy. However, the differences was not statistically significant. Conversely, total hip and femoral neck BMD improved significantly more in the combination therapy to denosumab monotherapy compared to teriparatide monotherapy to denosumab monotherapy or denosumab monotherapy to teriparatide monotherapy.

- **Certainty of evidence across all critical outcomes in GIOP population:** Very low

**TABLE 16. EVIDENCE AVAILABLE FOR COMBINATION THERAPY (TERIPARATIDE + DENOSUMAB) VS TERIPARATIDE OR DENOSUMAB ALONE IN GENERAL POPULATION**

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(TP/DN)	TP or DN only	Relative (95% CI)	Absolute (95% CI)		
Combination vs. Teriparatide Only												
Change in L- Spine BMD g/cm <sup>2</sup> _12 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	31	-	Mean Difference <b>2.9% higher</b> (0.6 higher to 5.1 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in L-Spine BMD g/cm <sup>2</sup> _24 months (Tsai, 2013)												



Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(TP/DN)	TP or DN only	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	31	-	Mean difference <b>3.4% higher</b> (0.66 higher to 6.14 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Femoral neck BMD g/cm <sup>2</sup> _12 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	31	-	Mean Difference <b>3.4% higher</b> (1.5 higher to 5.3 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Femoral neck BMD g/cm <sup>2</sup> _24 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	31	-	Mean Difference <b>4.0% higher</b> (2.12 higher to 5.88 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Total hip BMD g/cm <sup>2</sup> _12 months (Tsai, 2013)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(TP/DN)	TP or DN only	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	31	-	Mean Difference <b>4.2% higher</b> (2.8 higher to 5.6 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Total hip BMD g/cm <sup>2</sup> _24 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	31		Mean Difference <b>4.3% higher</b> (2.89 higher to 5.71 higher)	⊕○○○ Very low	FAVORS TP/DN
Combination vs. Denosumab												
Change in PA Lumbar Spine BMD g/cm <sup>2</sup> _12 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	33	-	Mean Difference <b>3.5 % higher</b> (1.6 higher to 5.4 higher)	⊕○○○ Very low	FAVORS TP/DN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(TP/DN)	TP or DN only	Relative (95% CI)	Absolute (95% CI)		
Change in PA Lumbar Spine BMD g/cm <sup>2</sup> _24 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	33		Mean Difference <b>3.6% higher</b> (2.05 higher to 5.15 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Femoral neck BMD g/cm <sup>2</sup> _12 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	33	-	Mean difference <b>2.1 % higher</b> (0.3 higher to 3.8 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Femoral neck BMD g/cm <sup>2</sup> _24 months (Tsai, 2013)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(TP/DN)	TP or DN only	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	33		Mean Difference <b>3.6 higher</b> (2.05 higher to 5.15 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Total Hip BMD g/cm <sup>2</sup> _12 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	33	-	Mean Difference <b>2.4 % higher</b> (1 higher to 3.8 higher)	⊕○○○ Very low	FAVORS TP/DN
Change in Total Hip BMD g/cm <sup>2</sup> _24 months (Tsai, 2013)												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	30	33		Mean Difference <b>3.1 higher</b> (1.84 higher to 4.36 higher)	⊕○○○ Very low	FAVORS TP/DN

CI: confidence interval; MD: mean difference

- a. Unclear allocation concealment and reporting bias. The trial is at high risk for reporting bias given its population is woman at high risk of fracture yet it does not report fracture outcomes. Outcome assessors were blinded to treatment.
- b. Indirect population and outcome.
- c. Single study with small sample size

**TABLE 17. EVIDENCE AVAILABLE ON SWITCHING COMBINATION (TERIPARATIDE + DENOSUMAB) TO DENOSUMAB ALONE IN GENERAL POPULATION**

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Leder et al. 2020  The DATA SWITCH Study	Long-term extension of DATA study	24 months	83 post-menopausal women at high-risk for fracture who completed the DATA study  <i>*Note, this study does not pertain to Sequential Therapy (PICOs 13.1-13.6) because in this study patients do not discontinue original therapy prior to switching to other therapy.</i>	After 24 months of treatment with teriparatide, denosumab, or combination teriparatide plus denosumab, women were transitioned to the following: <ul style="list-style-type: none"> <li>• Teriparatide monotherapy to denosumab monotherapy (n=27)</li> <li>• Denosumab monotherapy to teriparatide monotherapy (n=27)</li> <li>• Combination (teriparatide+denosumab) to denosumab monotherapy (n=23)</li> </ul>	Mean net 48 month increase in bone mineral density (BMD), from the original DATA study for 24 months to DATA SWITCH for another 24 months:  <b>Lumbar Spine BMD</b> <ul style="list-style-type: none"> <li>• Teriparatide only to denosumab only: 18.3% (standard deviation [SD] 8.5%) increase</li> <li>• Denosumab only to teriparatide only: 14.0% (SD: 6.7%) increase</li> <li>• Combination to denosumab only: 16.0% (SD: 4.1%) increase</li> </ul> *Differences between groups was not significant  <b>Total hip BMD</b> <ul style="list-style-type: none"> <li>• Teriparatide only to denosumab only: 6.6% (SD: 3.3%) increase</li> <li>• Denosumab only to teriparatide only: 2.7% (SD: 3.3%) increase</li> <li>• Combination to denosumab only: 8.6% (SD: 3.0%) increase</li> </ul>

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					<p>Significant difference between combination therapy to denosumab only and the other 2 groups (<math>p &lt; 0.05</math>)</p> <p><b>Femoral neck BMD</b></p> <ul style="list-style-type: none"> <li>• Teriparatide only to denosumab only: 0.0% (SD: 2.9%) increase</li> <li>• Denosumab only to teriparatide only: -1.8% (AD: 5.9%) increase</li> <li>• Combination to denosumab only: 2.8% (SD: 3.2%) increase</li> </ul> <p>Significant difference between combination therapy to denosumab only and the other 2 groups (<math>p &lt; 0.01</math>)</p> <p><b>Incidence of fracture not reported</b></p>

#### References:

1. Tsai, J. N., Uihlein, A. V., Lee, H., Kumbhani, R., Siwila-Sackman, E., McKay, E. A., & Leder, B. Z. (2013). Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *The Lancet*, 382(9886), 50-56.
2. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K, Lee H, Neer RM. Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab*. 2014 May;99(5):1694-700. doi: 10.1210/jc.2013-4440. Epub 2014 Feb 11. PMID: 24517156; PMCID: PMC4010689.
3. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, Burnett-Bowie SA. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet*. 2015 Sep 19;386(9999):1147-55. doi: 10.1016/S0140-6736(15)61120-5. Epub 2015 Jul 2. PMID: 26144908; PMCID: PMC4620731.

#### 1.32 What are the benefits or harms of using oral bisphosphonate plus PTH analog?

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate plus PTH analog, calcium, and vitamin D, versus treatment with one agent alone, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.33 What are the benefits or harms of using IV bisphosphonate plus PTH analog?**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate plus PTH analog, calcium, and vitamin D, versus treatment with one agent alone, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.34 What are the benefits or harms of using oral bisphosphonate plus romosozumab?**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate plus romosozumab, calcium, and vitamin D, versus treatment with one agent alone, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **1.35 What are the benefits or harms of using IV bisphosphonate plus romosozumab?**

In men and post-menopausal women  $\geq$  age 40 and who are continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate plus romosozumab, calcium, and vitamin D, versus treatment with one agent alone, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### III. MEN AND WOMEN (NOT OF CHILDBEARING POTENTIAL) UNDER 40 WITH ANY PAST FRAGILITY FRACTURE TREATMENT QUESTIONS

#### 2.1. Vit D+Ca vs Placebo

In adults < age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

- **Certainty of Evidence across all critical outcomes for GIOP Population: Very Low**

Table 18. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR VIT D+CA VS PLACEBO IN ADULTS UNDER 40

Bibliography: [Braun, et al. Clin Endocrinol \(Oxf\). 1983 Aug; 19\(2\): 265-73](#); <sup>[1]</sup> [Adachi, et al. J Rheumatol. 1996 Jun;23\(6\): 995-1000](#) <sup>[2]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
Hip Fracture			No data		
Vertebral Fracture	62 (1 RCT) 36 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	Relative Risk 0.6 (0.16 to 2.3)	161 per 1000	65 fewer per 1000 (from 135 fewer to 210 more)
36 months					
Vertebral Fracture	14 (1 RCT) 6 months	⊕⊖⊖⊖ <b>VERY LOW</b> <sup>2,3,4,5</sup> due to risk of bias, indirectness, imprecision	Relative Risk 3.0 (0.14 to 63.15)	0 per 1000	-
6 months					
Non-Vertebral Fracture	14 (1 RCT) 6 months	⊕⊖⊖⊖ <b>VERY LOW</b> <sup>2,3,4,5</sup> due to risk of bias, indirectness, imprecision	Relative Risk 0.33 (0.02 to 7.02)	143 per 1000	96 fewer per 1000 (from 140 fewer to 860 more)
6 months					
Serious			No data		



## Adverse Events

### Total Adverse Events

No data

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients receiving Calcium and Vitamin D in the Braun, et al. study received 1α-(OH) D3 (Etalpa), an active form of Vitamin D.

CI: Confidence interval; RR: Risk ratio;

**Table 19. EVIDENCE FOR GENERAL OSTEOPOROSIS POPULATION FOR VIT D+CA VS PLACEBO IN ADULTS UNDER 40**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
<b>Hip Fracture</b>	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.98</b> (0.77 to 1.25)	<b>11 per 1000</b> Over a mean of 4.5 years	<b>0 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Vertebral Fracture</b>	42,115 (3 RCTs) 3 to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.90</b> (0.74 to 1.09)	<b>10 per 1000</b> Over a mean of 5 years	<b>1 fewer per 1000</b> (from 3 fewer to 1 more)
<b>Non-Vertebral Fracture</b>	5,833 (2 RCTs) to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.93</b> (0.78 to 1.09)	<b>88 per 1000</b> Over a mean of 5 years	<b>6 fewer per 1000</b> (from 19 fewer to 8 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Grant, et al., Lancet. 2005 May 7-13; 365 \(9471\):1621-8](#) <sup>[3]</sup>; [Porthouse, et al. BMJ. 2005; 330\(7498\):1003](#) <sup>[4]</sup>; [Jackson, et al. N Engl J Med. 2006;354\(7\):669-83](#) <sup>[5]</sup>; [Salovaara, et al. J Bone Miner Res. 2010 Jul;25 \(7\):1487-95](#) <sup>[6]</sup>

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

## 2.2. Lifestyle vs Ca/Vit D

In adults < age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.3. Lifestyle+Ca/D vs Ca/Vit D

In adults < age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.4. Oral bisphosphonate vs Ca/Vit D

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 20. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATE VS CA/D FOR <40 WITH PAST FRAGILITY FRACTURE ON GLUCOCORTICOIDS**

**Bibliography:** [Saag, 1998](#) <sup>[11]</sup>; [Wallach, 2000](#) <sup>[12]</sup>; [Adachi, 2001](#) <sup>[13]</sup>; [Lems, 2006](#) <sup>[14]</sup>; [Yamada, 2007](#) <sup>[15]</sup>; [Okada, 2008](#) <sup>[16]</sup>; [Saadati, 2008](#) <sup>[17]</sup>; [Stoch, 2009](#) <sup>[18]</sup>; [Tee, 2012](#) <sup>[19]</sup>; [Hakala, 2012](#) <sup>[20]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D	Risk difference with Oral

				and Calcium alone*	Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	532 (5 RCTs)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3</sup>	<b>Relative Risk</b> <b>0.57</b> (0.09 to 3.56)	<b>9 per 1000</b>	<b>4 fewer per 1000</b> (from 8 fewer to 22 more)
<b>12 months</b>	12 months	due to risk of bias, imprecision			
<b>Vertebral Fracture</b>	202 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>4,5</sup>	<b>Relative Risk</b> <b>0.1</b> (0.01 to 0.9)	<b>68 per 1000</b>	<b>61 fewer per 1000</b> (from 7 fewer to 67 fewer)
<b>24 months</b>	24 months	due to risk of bias, imprecision			
<b>Vertebral Fracture</b>	1051 (7 RCTs)	⊕⊕⊕⊕ <b>LOW</b> <sup>2,3,6</sup>	<b>Relative Risk</b> <b>0.66</b> (0.25 to 1.77)	<b>69 per 1000</b>	<b>23 fewer per 1000</b> (from 52 fewer to 53 more)
<b>12 months</b>	12 months	due to risk of bias, imprecision			
<b>Non-Vertebral Fracture</b>	208 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>4,5</sup>	<b>Relative Risk</b> <b>0.55</b> (0.2 to 1.53)	<b>98 per 1000</b>	<b>44 fewer per 1000</b> (from 79 fewer to 52 more)
<b>24 months</b>	24 months	due to risk of bias, imprecision			
<b>Non-Vertebral Fracture</b>	1353 (7 RCTs)	⊕⊕⊕⊕ <b>LOW</b> <sup>3,7,8</sup>	<b>Relative Risk</b> <b>0.89</b> (0.52 to 1.53)	<b>43 per 1000</b>	<b>5 fewer per 1000</b> (from 21 fewer to 23 more)
<b>12 months</b>	12 months	due to risk of bias, imprecision			
<b>Serious Adverse Events</b>	1192 (7 RCTs)	⊕⊕⊕⊕ <b>LOW</b> <sup>2,3,7</sup>	<b>Relative Risk</b> <b>0.95</b> (0.76 to 1.18)	<b>213 per 1000</b>	<b>11 fewer per 1000</b> (from 51 fewer to 38 more)
	12 months	due to risk of bias, imprecision			
<b>Total Adverse Events</b>	848 (6 RCTs)	⊕⊕⊕⊕ <b>MODERATE</b> <sup>7</sup>	<b>Relative Risk</b> <b>0.97</b> (0.9 to 1.05)	<b>753 per 1000</b>	<b>23 fewer per 1000</b> (from 75 fewer to 38 more)
	12 months	due to risk of bias			
<b>Upper GI Adverse Events</b>	996 (4 RCTs)	⊕⊕⊕⊕ <b>MODERATE</b> <sup>7</sup>	<b>Relative Risk</b> <b>1.14</b> (0.88 to 1.48)	<b>184 per 1000</b>	<b>26 more per 1000</b> (from 22 fewer to 88 more)
	12 months	due to risk of bias			

<sup>1</sup> 4/5 studies were rated "high risk of bias" in at least one category. 3 studies were "high risk of bias" in at least 2 categories

<sup>2</sup> 3 studies had effects with wide 95% CI.

<sup>3</sup> The effect of at least one study is inestimable due to zero events

<sup>4</sup> Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

<sup>5</sup> Outcome is only assessed by one study

<sup>6</sup> 2/7 studies are open label. More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>7</sup> More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>8</sup> 4 studies have very wide 95% CI

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

**TABLE 21. EVIDENCE AVAILABLE FOR ORAL BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION <40 YEARS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	21,811 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.71</b> (0.55 to 0.91)	<b>19 per 1000</b> Over a mean of 2.5 years	<b>6 fewer per 1000</b> (from 2 fewer to 8 fewer)
<b>Vertebral Fracture</b>	10,500 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.59</b> (0.51 to 0.68)	<b>88 per 1000</b> Over a mean of 2.5 years	<b>36 fewer per 1000</b> (from 28 fewer to 43 fewer)
<b>Non-Vertebral Fracture</b>	22,022 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.84</b> (0.77 to 0.91)	<b>106 per 1000</b> Over a mean of 2.5 years	<b>17 fewer per 1000</b> (from 10 fewer to 24 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Cochrane Database Syst Rev. 2008 Jan 23; \(1\):CD001155 \[21\]](#); [Cochrane Database Syst Rev. 2008 Jan 23; \(1\):CD004523 \[22\]](#)

## 2.5. IV bisphosphonate vs Ca/Vit D

In adults <age 40 with any past fragility fracture at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**Table 22. EVIDENCE AVAILABLE FOR IV BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION <40 YEARS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <sup>1</sup> MODERATE	Relative Risk 0.70 (0.42 to 1.17)	23 per 1000 Over 3 years	7 fewer per 1000 (from 13 fewer to 4 more)
Vertebral Fracture	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <sup>1</sup> MODERATE	Relative Risk 0.57 (0.35 to 0.91)	109 per 1000 Over 3 years	47 fewer per 1000 (from 10 fewer to 71 fewer)
Non-Vertebral Fracture	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <sup>1</sup> MODERATE	Relative Risk 0.74 (0.56 to 0.94)	100 per 1000 Over 3 years	26 fewer per 1000 (from 6 fewer to 44 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 209](#) <sup>[23]</sup>; [Lyles, et al., N Engl J Med. 2007; 357\(18\):1799-809](#) <sup>[24]</sup>.

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

## 2.6. Teriparatide vs Ca/Vit D

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

TABLE 23. EVIDENCE AVAILABLE FOR TERIPARATIDE IN GENERAL OSTEOPOROSIS POPULATION <40 YEARS

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and	Risk difference with

				Vitamin D alone*	Teriparatide (95% CI)**
<b>Hip Fracture</b>	1,637 (1 RCT) 2 years	⊕⊕⊖⊖ <b>LOW</b>	<b>Relative Risk 0.50</b> (0.09 to 2.73)	<b>7 per 1000</b> Over 2 years	<b>4 fewer per 1000</b> (from 6 fewer to 12 more)
<b>Vertebral Fracture</b>	4,359 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b>	<b>Relative Risk 0.36</b> (0.28 to 0.47)	<b>143 per 1000</b> Over 2 years	<b>92 fewer per 1000</b> (from 76 fewer to 103 fewer)
<b>Non-Vertebral Fracture</b>	2,377 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b>	<b>Relative Risk 0.62</b> (0.48 to 0.82)	<b>97 per 1000</b> Over 2 years	<b>37 fewer per 1000</b> (from 18 fewer to 50 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#) <sup>[23]</sup>; [Neer, et al., N Engl J Med. 2001 May 10; 344\(19\):1434-41](#) <sup>[29]</sup>; [Stevenson, et al. Health Technol Assess. 2005 Jun;9\(22\):1-160](#) <sup>[30]</sup>; [Vestergaard, et al. Osteoporos Int. 2007 Jan;18\(1\):45-57](#) <sup>[31]</sup>

## 2.7 Abaloparatide vs Ca/Vit D

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.8. Denosumab vs Ca/Vit D

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 24. EVIDENCE AVAILABLE FOR DENOSUMAB IN GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants	Certainty of the evidence	Relative effect	Anticipated absolute effects
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	(studies) Follow up	(GRADE)	(95% CI)	Risk with Calcium and Vitamin D alone*	Risk difference with Denosumab (95% CI)**
<b>Hip Fracture</b>	7,297 (1 RCT) 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk 0.59</b> (0.36 to 0.94)	<b>11 per 1000</b> Over 3 years	<b>5 fewer per 1000</b> (from 1 fewer to 7 fewer)
<b>Vertebral Fracture</b>	7,738 (2 RCTs) 2 to 3 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.32</b> (0.25 to 0.41)	<b>72 per 1000</b> Over 3 years	<b>49 fewer per 1000</b> (from 43 fewer to 54 fewer)
<b>Non-Vertebral Fracture</b>	7,657 (2 RCTs) 2 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>2</sup> due to imprecision	<b>Relative Risk 0.65</b> (0.28 to 1.51)	<b>75 per 1000</b> Over 3 years	<b>26 fewer per 1000</b> (from 54 fewer to 38 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#); <sup>[23]</sup> [Bone, et al. J Clin Endocrinol Metab. 2008; 93 \(6\):2149-57](#) <sup>[32]</sup>; [Cummings, et al. N Engl J Med. 2009 Aug 20; 361 \(8\):756-65](#) <sup>[33]</sup>

<sup>1</sup> Outcome is only assessed by one study

<sup>2</sup> 95% CI of one trial passes beyond the other and passes null effect

## 2.9 Romosozumab vs Ca/Vit D

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.10. IV bisphosphonate vs Oral bisphosphonate

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

TABLE 25. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATE VS ORAL BISPHOSPHONATE < 40 WITH PAST FRAGILITY FRACTURE

**Bibliography:** [Reid, et al. Lancet. 2009 Apr 11; 373\(9671\): 1253-63](#) <sup>[34]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture 12 months	833 (1 RCT) 12 months	⊕⊕⊖⊖⊖ LOW <sup>1,2,3</sup> due to imprecision	Relative Risk 1.67 (0.4 to 6.95)	7 per 1000	5 more per 1000 (from 4 fewer to 43 more)
Non-Vertebral Fracture					
			No data		
Serious Adverse Events	833 (1 RCT) 12 months	⊕⊕⊖⊖⊖ LOW <sup>1,3</sup> due to imprecision	Relative Risk 0.99 (0.74 to 1.32)	185 per 1000	2 fewer per 1000 (from 48 fewer to 59 more)
Total Adverse Events	833 (1 RCT) 12 months	⊕⊕⊖⊖⊖ LOW <sup>1,3</sup> due to imprecision	Relative Risk 1.16 (1.06 to 1.26)	669 per 1000	107 more per 1000 (from 40 more to 174 more)

**Bibliography:** [Reid, et al. Lancet. 2009 Apr 11; 373\(9671\): 1253-63](#) <sup>[34]</sup>

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

<sup>3</sup> Per Panel Request, Reid 2009 was downgraded from an original grade of “Moderate” to a new grade of “Low” (5/14/16)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

**TABLE 26. EVIDENCE AVAILABLE FOR IV BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
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Follow up			Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture			No data	
Vertebral Fracture	131 (2 RCTs) 1 year	⊕⊕⊕⊕ VERY LOW	Relative Risk 1.50 (0.29 to 7.73)	31 per 1000 Over 1 year
Non-Vertebral Fracture			No data	15 more per 1000 (from 22 fewer to 207 more)
Bibliography: <a href="#">Crandall, et al. AHRQ CER 53, March 2012</a> ; <a href="#">Tauchmanová, et al. Bone Marrow Transplant. 2006 Jan; 37 (1):81-8</a> <sup>[35]</sup> ; <a href="#">Chávez-Valencia, et al. J Clin Densitom. 2014 Oct-Dec;17(4):484-9</a> <sup>[36]</sup>				
Note: Explanation for downgrade not provided in previous evidence review.				

## 2.11. Teriparatide vs Oral bisphosphonate

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

**TABLE 27. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR TERIPARATIDE VS ORAL BISPHOSPHONATE IN ADULTS <40 WITH PAST FRAGILITY FRACTURE**

Bibliography: [Saag, et al. N Engl J Med. 2007 Nov 15; 357\(20\): 2028-39](#) <sup>[38]</sup>. [Saag, et al. Arthritis Rheum. 2009 Nov; 60\(11\): 3346-55](#) <sup>[39]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate *	Risk difference with Teriparatide (95% CI)**
Hip Fracture	428 (1 RCT)	⊕⊕⊕⊕ LOW <sup>1,2,3,5</sup>	Relative Risk 0.33 (0.01 to 8.14)	5 per 1000	3 fewer per 1000 (from 5 fewer to 33 more)
18 months	18 months	due to risk of bias, imprecision			

<b>Vertebral Fracture</b>	342 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to imprecision	<b>Relative Risk</b> <b>0.23</b> (0.07 to 0.78)	<b>77 per 1000</b>	<b>59 fewer per 1000</b> (from 17 fewer to 72 fewer)
<b>36 months</b>	36 months				
<b>Vertebral Fracture</b>	336 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,5</sup> due to imprecision	<b>Relative Risk</b> <b>0.1</b> (0.01 to 0.75)	<b>61 per 1000</b>	<b>55 fewer per 1000</b> (from 15 fewer to 60 fewer)
<b>18 months</b>	18 months				
<b>Non-Vertebral Fracture</b>	428 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>1.07</b> (0.54 to 2.1)	<b>70 per 1000</b>	<b>5 more per 1000</b> (from 32 fewer to 77 more)
<b>36 months</b>	36 months				
<b>Non-Vertebral Fracture</b>	428 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3,5</sup> due to imprecision	<b>Relative Risk</b> <b>1.5</b> (0.63 to 3.6)	<b>37 per 1000</b>	<b>19 more per 1000</b> (from 14 fewer to 97 more)
<b>18 months</b>	18 months				
<b>Serious Adverse Events</b>	428 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to imprecision	<b>Relative Risk</b> <b>1.06</b> (0.87 to 1.28)	<b>299 per 1000</b>	<b>18 more per 1000</b> (from 39 fewer to 84 more)
	36 months				
<b>Total Adverse Events</b>	428 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to imprecision	<b>Relative Risk</b> <b>1.05</b> (0.98 to 1.13)	<b>860 per 1000</b>	<b>43 more per 1000</b> (from 17 fewer to 112 more)
	36 months				

<sup>1</sup> 31% discontinuation rate at 18 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> 95% CI is wide

<sup>4</sup> 44% discontinuation rate at 36 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>5</sup> Per Panel Request, Saag 2007 and Saag 2009 were downgraded from an original grade of “Moderate” to a new grade of “Low” due to small sample size and incredible treatment effects (5/14/16)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

**Table 28. EVIDENCE AVAILABLE FOR TERIPARATIDE IN GENERAL OSTEOPOROSIS POPULATION FOR ADULTS <40**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture	146 (1 RCT) 1 year	⊕⊕⊖⊖ LOW	Relative Risk 0.30 (0.09 to 1.05)	137 per 1000 Over 1 year	96 fewer per 1000 (from 125 fewer to 7 more)
Bibliography: <a href="#">Crandall, et al. AHRQ CER 53, March 2012</a> ; <a href="#">Body, et al. J Clin Endocrinol Metab. 2002 Oct;87(10):4528-35</a> <sup>[40]</sup>					

## 2.12 Abaloparatide vs Oral bisphosphonate

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.13. Denosumab vs Oral bisphosphonate

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.14 Romosozumab vs Oral bisphosphonate

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **2.15. Teri vs IV bisphosphonate**

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D ?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **2.16 Abaloparatide vs IV bisphosphonate**

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **2.17. Denosumab vs IV bisphosphonate**

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D ?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **2.18 Romosozumab vs IV bisphosphonate**

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D ?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **2.19. Denosumab vs Teriparatide**

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with teriparatide, calcium, and vitamin D ?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.20 Denosumab vs Abaloparatide

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with abaloparatide, calcium, and vitamin D ?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 2.21 Denosumab vs. Romosozumab

In adults <age 40 with any past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with romosozumab, calcium, and vitamin D ?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## ***IV. MEN AND WOMEN (NOT OF CHILDBEARING POTENTIAL) UNDER 40 WITH BMD Z SCORE < -3 AT HIP OR SPINE BUT NO PAST FRAGILITY FRACTURE TREATMENT QUESTIONS***

### 3.1. Vit D+Ca vs Placebo

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

- **Certainty of evidence for all critical outcomes for GIOP population: Very Low**

**TABLE 29. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR UNDER 40 WITH BMD Z SCORE < -3 (NO PAST FRAGILITY FRACTURE)**

**Bibliography:** [Braun, et al. Clin Endocrinol \(Oxf\). 1983 Aug; 19\(2\): 265-73†;\[1\]](#) [Adachi, et al. J Rheumatol. 1996 Jun;23\(6\): 995-1000 \[2\]](#)

Outcomes	No of	Certainty of the evidence	Relative effect	Anticipated absolute effects
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	Participants (GRADE) (studies) Follow up	(95% CI)	Risk with No Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
Hip Fracture				
			No data	
Vertebral Fracture 36 months	62 (1 RCT) 36 months	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	Relative Risk <b>0.6</b> (0.16 to 2.3)	<b>161 per 1000</b>  <b>65 fewer per 1000</b> (from 135 fewer to 210 more)
Vertebral Fracture 6 months	14 (1 RCT) 6 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>2,3,4,5</sup> due to risk of bias, indirectness, imprecision	Relative Risk <b>3</b> (0.14 to 63.15)	<b>0 per 1000</b>  -
Non-Vertebral Fracture 6 months	14 (1 RCT) 6 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>2,3,4,5</sup> due to risk of bias, indirectness, imprecision	Relative Risk <b>0.33</b> (0.02 to 7.02)	<b>143 per 1000</b>  <b>96 fewer per 1000</b> (from 140 fewer to 860 more)
Serious Adverse Events				
			No data	
Total Adverse Events				
			No data	

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients receiving Calcium and Vitamin D in the Braun, et al. study received 1α-(OH) D3 (Etalpa), an active form of Vitamin D.

**CI:** Confidence interval; **RR:** Risk ratio;

**Table 30. EVIDENCE FOR GENERAL OSTEOPOROSIS POPULATION ADULTS UNDER 40 WITH BMD Z SCORE < -3 (NO PAST FRAGILITY FRACTURE)**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
<b>Hip Fracture</b>	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.98</b> (0.77 to 1.25)	<b>11 per 1000</b> Over a mean of 4.5 years	<b>0 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Vertebral Fracture</b>	42,115 (3 RCTs) 3 to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.90</b> (0.74 to 1.09)	<b>10 per 1000</b> Over a mean of 5 years	<b>1 fewer per 1000</b> (from 3 fewer to 1 more)
<b>Non-Vertebral Fracture</b>	5,833 (2 RCTs) to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.93</b> (0.78 to 1.09)	<b>88 per 1000</b> a mean of 5 years	<b>Over 6 fewer per 1000</b> (from 19 fewer to 8 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Grant, et al., Lancet. 2005 May 7-13; 365 \(9471\):1621-8 \[3\]](#); [Porthouse, et al. BMJ. 2005; 330\(7498\):1003 \[4\]](#); [Jackson, et al. N Engl J Med. 2006;354\(7\):669-83 \[5\]](#); [Salovaara, et al. J Bone Miner Res. 2010 Jul;25 \(7\):1487-95 \[6\]](#)

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

### 3.2. Lifestyle vs Ca/Vit D

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.3. Lifestyle+CA/D vs Ca/Vit D

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.4. Oral bisphosphonate vs Ca/Vit D

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- **Certainty of evidence for all critical outcomes for GIOP population: Moderate (Adverse event data only)**

**TABLE 31. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATE VS CALCIUM/VITAMIN D IN ADULTS <40 WITHOUT FRAGILITY FRACTURE WITH BMD<-3**

**Bibliography:** [Saag, 1998](#) <sup>[11]</sup>; [Wallach, 2000](#) <sup>[12]</sup>; [Adachi, 2001](#) <sup>[13]</sup>; [Lems, 2006](#) <sup>[14]</sup>; [Yamada, 2007](#) <sup>[15]</sup>; [Okada, 2008](#) <sup>[16]</sup>; [Saadati, 2008](#) <sup>[17]</sup>; [Stoch, 2009](#) <sup>[18]</sup>; [Tee, 2012](#) <sup>[19]</sup>; [Hakala, 2012](#) <sup>[20]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D and Calcium alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b> <b>12 months</b>	532 (5 RCTs) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk 0.57</b> (0.09 to 3.56)	<b>9 per 1000</b>	<b>4 fewer per 1000</b> (from 8 fewer to 22 more)
<b>Vertebral Fracture</b> <b>24 months</b>	202 (1 RCT) 24 months	⊕⊕⊖⊖ <b>LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.1</b> (0.01 to 0.9)	<b>68 per 1000</b>	<b>61 fewer per 1000</b> (from 7 fewer to 67 fewer)
<b>Vertebral Fracture</b> <b>12 months</b>	1051 (7 RCTs) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,3,6</sup> due to risk of bias,	<b>Relative Risk 0.66</b> (0.25 to 1.77)	<b>69 per 1000</b>	<b>23 fewer per 1000</b> (from 52 fewer to 53 more)



		imprecision			
<b>Non-Vertebral Fracture</b>	208 (1 RCT) 24 months	⊕⊕⊕⊕ <b>LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.55</b> (0.2 to 1.53)	<b>98 per 1000</b>	<b>44 fewer per 1000</b> (from 79 fewer to 52 more)
<b>24 months</b>					
<b>Non-Vertebral Fracture</b>	1353 (7 RCTs) 12 months	⊕⊕⊕⊕ <b>LOW</b> <sup>3,7,8</sup> due to risk of bias, imprecision	<b>Relative Risk 0.89</b> (0.52 to 1.53)	<b>43 per 1000</b>	<b>5 fewer per 1000</b> (from 21 fewer to 23 more)
<b>12 months</b>					
<b>Serious Adverse Events</b>	1192 (7 RCTs) 12 months	⊕⊕⊕⊕ <b>LOW</b> <sup>2,3,7</sup> due to risk of bias, imprecision	<b>Relative Risk 0.95</b> (0.76 to 1.18)	<b>213 per 1000</b>	<b>11 fewer per 1000</b> (from 51 fewer to 38 more)
<b>Total Adverse Events</b>	848 (6 RCTs) 12 months	⊕⊕⊕⊕ <b>MODERATE</b> <sup>7</sup> due to risk of bias	<b>Relative Risk 0.97</b> (0.9 to 1.05)	<b>753 per 1000</b>	<b>23 fewer per 1000</b> (from 75 fewer to 38 more)
<b>Upper GI Adverse Events</b>	996 (4 RCTs) 12 months	⊕⊕⊕⊕ <b>MODERATE</b> <sup>7</sup> due to risk of bias	<b>Relative Risk 1.14</b> (0.88 to 1.48)	<b>184 per 1000</b>	<b>26 more per 1000</b> (from 22 fewer to 88 more)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> 4/5 studies were rated "high risk of bias" in at least one category. 3 studies were "high risk of bias" in at least 2 categories

<sup>2</sup> 3 studies had effects with wide 95% CI.

<sup>3</sup> The effect of at least one study is inestimable due to zero events

<sup>4</sup> Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

<sup>5</sup> Outcome is only assessed by one study

<sup>6</sup> 2/7 studies are open label. More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>7</sup> More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>8</sup> 4 studies have very wide 95% CI

**TABLE 32. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION BISPHOSPHONATE VS CALCIUM/VITAMIN D IN ADULTS <40 WITHOUT FRAGILITY FRACTURE WITH BMD<-3**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Oral Bisphosphonate (95% CI)**
Hip Fracture	21,811 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ HIGH	Relative Risk 0.71 (0.55 to 0.91)	19 per 1000 Over a mean of 2.5 years	6 fewer per 1000 (from 2 fewer to 8 fewer)
Vertebral Fracture	10,500 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ HIGH	Relative Risk 0.59 (0.51 to 0.68)	88 per 1000 Over a mean of 2.5 years	36 fewer per 1000 (from 28 fewer to 43 fewer)
Non-Vertebral Fracture	22,022 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ HIGH	Relative Risk 0.84 (0.77 to 0.91)	106 per 1000 Over a mean of 2.5 years	17 fewer per 1000 (from 10 fewer to 24 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Cochrane Database Syst Rev. 2008 Jan 23; \(1\):CD001155](#).<sup>[21]</sup>; [Cochrane Database Syst Rev. 2008 Jan 23; \(1\):CD004523](#) <sup>[22]</sup>

### 3.5. IV bisphosphonate vs Ca/Vit D

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- Certainty of evidence across all critical outcomes for GIOP population: Very low

**TABLE 33. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION IV BISPHOSPHONATE VS CALCIUM/VITAMIN D IN ADULTS <40 WITHOUT FRAGILITY FRACTURE WITH BMD<-3**

Evidence Available for General Osteoporosis Population:				
Outcomes	No of Participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects

Follow up				Risk with Calcium and Vitamin D alone*	Risk difference with IV Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.70</b> (0.42 to 1.17)	<b>23 per 1000</b> Over 3 years	<b>7 fewer per 1000</b> (from 13 fewer to 4 more)
<b>Vertebral Fracture</b>	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.57</b> (0.35 to 0.91)	<b>109 per 1000</b> Over 3 years	<b>47 fewer per 1000</b> (from 10 fewer to 71 fewer)
<b>Non-Vertebral Fracture</b>	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.74</b> (0.56 to 0.94)	<b>100 per 1000</b> Over 3 years	<b>26 fewer per 1000</b> (from 6 fewer to 44 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#) <sup>[23]</sup>; [Lyles, et al., N Engl J Med. 2007; 357\(18\):1799-809](#) <sup>[24]</sup>.

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

### 3.6. Teriparatide vs Ca/Vit D

In adults < age 40, with closed growth plates, without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 34. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION TERIPARATIDE VS CALCIUM/VITAMIN D IN ADULTS <40 WITHOUT FRAGILITY FRACTURE WITH BMD<-3**

Outcomes	No of Participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
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Follow up				Risk with Calcium and Vitamin D alone*	Risk difference with Teriparatide (95% CI)**
<b>Hip Fracture</b>	1,637 (1 RCT) 2 years	⊕⊕⊕⊖ <b>LOW</b>	<b>Relative Risk 0.50</b> (0.09 to 2.73)	<b>7 per 1000</b> Over 2 years	<b>4 fewer per 1000</b> (from 6 fewer to 12 more)
<b>Vertebral Fracture</b>	4,359 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b>	<b>Relative Risk 0.36</b> (0.28 to 0.47)	<b>143 per 1000</b> Over 2 years	<b>92 fewer per 1000</b> (from 76 fewer to 103 fewer)
<b>Non-Vertebral Fracture</b>	2,377 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b>	<b>Relative Risk 0.62</b> (0.48 to 0.82)	<b>97 per 1000</b> Over 2 years	<b>37 fewer per 1000</b> (from 18 fewer to 50 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209](#) <sup>[23]</sup>; [Neer, et al., N Engl J Med. 2001 May 10; 344\(19\):1434-41](#) <sup>[29]</sup>; [Stevenson, et al. Health Technol Assess. 2005 Jun;9\(22\):1-160](#) <sup>[30]</sup>; [Vestergaard, et al. Osteoporos Int. 2007 Jan;18\(1\):45-57](#) <sup>[31]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

### 3.7. Denosumab vs Ca/Vit D

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 35. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION DENOSUMAB VS CALCIUM/VITAMIN D IN ADULTS <40 WITHOUT FRAGILITY FRACTURE WITH BMD<-3**

Outcomes	No of Participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
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Follow up				Risk with Calcium and Vitamin D alone*	Risk difference with Denosumab (95% CI)**
<b>Hip Fracture</b>	7,297 (1 RCT) 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk 0.59</b> (0.36 to 0.94)	<b>11 per 1000</b> Over 3 years	<b>5 fewer per 1000</b> (from 1 fewer to 7 fewer)
<b>Vertebral Fracture</b>	7,738 (2 RCTs) 2 to 3 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.32</b> (0.25 to 0.41)	<b>72 per 1000</b> Over 3 years	<b>49 fewer per 1000</b> (from 43 fewer to 54 fewer)
<b>Non-Vertebral Fracture</b>	7,657 (2 RCTs) 2 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>2</sup> due to imprecision	<b>Relative Risk 0.65</b> (0.28 to 1.51)	<b>75 per 1000</b> Over 3 years	<b>26 fewer per 1000</b> (from 54 fewer to 38 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012;](#) [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209;](#)<sup>[23]</sup> [Bone, et al. J Clin Endocrinol Metab. 2008; 93 \(6\):2149-57](#)<sup>[32]</sup>; [Cummings, et al. N Engl J Med. 2009 Aug 20; 361 \(8\):756-65](#)<sup>[33]</sup>

<sup>1</sup> Outcome is only assessed by one study

<sup>2</sup> 95% CI of one trial passes beyond the other and passes null effect

### 3.8. IV bis vs Oral bisphosphonate

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 36. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR IV BISPHOSPHONATE VS ORAL BISPHOSPHONATE FOR ADULTS < AGE 40 WITHOUT PAST FRAGILITY FRACTURE BUT WITH BMD Z SCORE < -3**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
<b>Hip Fracture</b>			No data		

<b>Vertebral Fracture</b>	833 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3</sup>	<b>Relative Risk 1.67</b> (0.4 to 6.95)	<b>7 per 1000</b>	<b>5 more per 1000</b> (from 4 fewer to 43 more)
<b>12 months</b>	12 months	due to imprecision			
<b>Non-Vertebral Fracture</b>	No data				
<b>Serious Adverse Events</b>	833 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,3</sup>	<b>Relative Risk 0.99</b> (0.74 to 1.32)	<b>185 per 1000</b>	<b>2 fewer per 1000</b> (from 48 fewer to 59 more)
	12 months	due to imprecision			
<b>Total Adverse Events</b>	833 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,3</sup>	<b>Relative Risk 1.16</b> (1.06 to 1.26)	<b>669 per 1000</b>	<b>107 more per 1000</b> (from 40 more to 174 more)
	12 months	due to imprecision			

**Bibliography:** [Reid, et al. Lancet. 2009 Apr 11; 373\(9671\): 1253-63](#) <sup>[34]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

<sup>3</sup> Per Panel Request, Reid 2009 was downgraded from an original grade of “Moderate” to a new grade of “Low” (5/14/16)

**TABLE 37. EVIDENCE AVAILABLE FOR IV BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION**

<b>Outcomes</b>	<b>No of Participants (studies)</b> Follow up	<b>Certainty of the evidence (GRADE)</b>	<b>Relative effect (95% CI)</b>	<b>Anticipated absolute effects</b>	
				<b>Risk with Oral Bisphosphonate*</b>	<b>Risk difference with IV Bisphosphonate (95% CI)**</b>
<b>Hip Fracture</b>			No data		
<b>Vertebral Fracture</b>	131 (2 RCTs)	⊕⊕⊕⊕ <sup>1,2,3</sup> <b>VERY LOW</b>	<b>Relative Risk 1.50</b> (0.29 to 7.73)	<b>31 per 1000</b> Over 1 year	<b>15 more per 1000</b> (from 22 fewer to 207 more)
	1 year				

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**Non-Vertebral Fracture**

No data

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**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Tauchmanová, et al. Bone Marrow Transplant. 2006 Jan; 37 \(1\):81-8 \[35\]](#); [Chávez-Valencia, et al. J Clin Densitom. 2014 Oct-Dec;17\(4\):484-9 \[36\]](#)

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<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

<sup>3</sup> Per Panel Request, Reid 2009 was downgraded from an original grade of “Moderate” to a new grade of “Low” (5/14/16)

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### 3.9. Teriparatide vs Oral bisphosphonate

In adults < age 40, with closed growth plates, without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very lo**

### 3.10 Abaloparatide vs oral bisphosphonate

In adults < age 40, with closed growth plates, without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.11. Denosumab vs Oral bisphosphonate

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.12 ROMO vs oral bisphosphonate

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.13. Teri vs IV bisphosphonate

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.14 Abaloparatide vs IV bisphosphonate

In adults < age 40, with closed growth plates, without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.15. Den vs IV bisphosphonate

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**



### 3.16. Den vs Teriparatide

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with teriparatide, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 3.17 ROMO vs IV bisphosphonate

In adults < age 40 without past fragility fracture but with BMD Z score < -3 at hip or spine, and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## IV. MEN AND WOMEN (NOT OF CHILDBEARING POTENTIAL) UNDER 40 WITH NEITHER BMD Z SCORE < -3 AT HIP OR SPINE NOR ANY PAST FRAGILITY FRACTURE TREATMENT QUESTIONS

### 4.1.a. Vit D+Ca vs Placebo

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

- **Certainty of Evidence for GIOP Population: Very Low**

**TABLE 38. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR VIT D+CA VS PLACEBO IN ADULTS UNDER 40 WITH NO BMD Z SCORE <3 OR PAST FRAGILITY FRACTURE**

**Bibliography:** [Braun, et al. Clin Endocrinol \(Oxf\). 1983 Aug; 19\(2\): 265-73+;](#)<sup>[1]</sup> [Adachi, et al. J Rheumatol. 1996 Jun;23\(6\): 995-1000](#) <sup>[2]</sup>

Outcomes	No of Participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium and Vitamin D

Follow up				Supplementation (95% CI)**	
<b>Hip Fracture</b>				No data	
<b>Vertebral Fracture</b>	62 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk 0.6</b> (0.16 to 2.3)	<b>161 per 1000</b>	<b>65 fewer per 1000</b> (from 135 fewer to 210 more)
<b>36 months</b>	36 months				
<b>Vertebral Fracture</b>	14 (1 RCT)	⊕⊖⊖⊖ <b>VERY LOW</b> <sup>2,3,4,5</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk 3.0</b> (0.14 to 63.15)	<b>0 per 1000</b>	-
<b>6 months</b>	6 months				
<b>Non-Vertebral Fracture</b>	14 (1 RCT)	⊕⊕⊕⊖ <b>VERY LOW</b> <sup>2,3,4,5</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk 0.33</b> (0.02 to 7.02)	<b>143 per 1000</b>	<b>96 fewer per 1000</b> (from 140 fewer to 860 more)
<b>6 months</b>	6 months				
<b>Serious Adverse Events</b>				No data	
<b>Total Adverse Events</b>				No data	

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients receiving Calcium and Vitamin D in the Braun, et al. study received 1α-(OH) D3 (Etalpa), an active form of Vitamin D.

CI: Confidence interval; RR: Risk ratio

**TABLE 39. EVIDENCE FOR GENERAL OSTEOPOROSIS POPULATION FOR VIT D+CA VS PLACEBO IN ADULTS UNDER 40 WITH NO BMD Z SCORE <3 OR PAST FRAGILITY FRACTURE**

Outcomes	No of Participants	Certainty of the	Relative effect	Anticipated absolute effects
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	(studies) Follow up	evidence (GRADE)	(95% CI)	Risk with No Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
<b>Hip Fracture</b>	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.98</b> (0.77 to 1.25)	<b>11 per 1000</b> Over a mean of 4.5 years	<b>0 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Vertebral Fracture</b>	42,115 (3 RCTs) 3 to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.90</b> (0.74 to 1.09)	<b>10 per 1000</b> Over a mean of 5 years	<b>1 fewer per 1000</b> (from 3 fewer to 1 more)
<b>Non-Vertebral Fracture</b>	5,833 (2 RCTs) 3 to 7 years	⊕⊕⊕⊖ <sup>1</sup> <b>MODERATE</b>	<b>Relative Risk 0.93</b> (0.78 to 1.09)	<b>88 per 1000</b> Over a mean of 5 years	<b>6 fewer per 1000</b> (from 19 fewer to 8 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Grant, et al., Lancet. 2005 May 7-13; 365 \(9471\):1621-8 \[3\]](#); [Porthouse, et al. BMJ. 2005; 330\(7498\):1003 \[4\]](#); [Jackson, et al. N Engl J Med. 2006;354\(7\):669-83 \[5\]](#); [Salovaara, et al. J Bone Miner Res. 2010 Jul;25 \(7\):1487-95 \[6\]](#)

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

#### 4.2.a. lifestyle vs Ca/Vit D

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 4.3.a. lifestyle+CA/D vs Ca/Vit D

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 4.4.a. Oral bisphosphonate vs Ca/Vit D

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Moderate (based only on adverse events)**

**TABLE 40. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATE < AGE 40 WITHOUT PAST FRAGILITY FRACTURE AND WITHOUT BMD Z SCORE < -3**

**Bibliography:** [Saag, 1998](#) <sup>[11]</sup>; [Wallach, 2000](#) <sup>[12]</sup>; [Adachi, 2001](#) <sup>[13]</sup>; [Lems, 2006](#) <sup>[14]</sup>; [Yamada, 2007](#) <sup>[15]</sup>; [Okada, 2008](#) <sup>[16]</sup>; [Saadati, 2008](#) <sup>[17]</sup>; [Stoch, 2009](#) <sup>[18]</sup>; [Tee, 2012](#) <sup>[19]</sup>; [Hakala, 2012](#) <sup>[20]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D and Calcium alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b> <b>12 months</b>	532 (5 RCTs) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk 0.57</b> (0.09 to 3.56)	<b>9 per 1000</b>	<b>4 fewer per 1000</b> (from 8 fewer to 22 more)
<b>Vertebral Fracture</b> <b>24 months</b>	202 (1 RCT) 24 months	⊕⊕⊖⊖ <b>LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.1</b> (0.01 to 0.9)	<b>68 per 1000</b>	<b>61 fewer per 1000</b> (from 7 fewer to 67 fewer)
<b>Vertebral Fracture</b> <b>12 months</b>	1051 (7 RCTs) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,3,6</sup> due to risk of bias, imprecision	<b>Relative Risk 0.66</b> (0.25 to 1.77)	<b>69 per 1000</b>	<b>23 fewer per 1000</b> (from 52 fewer to 53 more)
<b>Non-Vertebral Fracture</b> <b>24 months</b>	208 (1 RCT) 24 months	⊕⊕⊖⊖ <b>LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.55</b> (0.2 to 1.53)	<b>98 per 1000</b>	<b>44 fewer per 1000</b> (from 79 fewer to 52 more)

<b>Non-Vertebral Fracture</b>	1353 (7 RCTs) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>3,7,8</sup> due to risk of bias, imprecision	<b>Relative Risk 0.89</b> (0.52 to 1.53)	<b>43 per 1000</b>	<b>5 fewer per 1000</b> (from 21 fewer to 23 more)
<b>12 months</b>					
<b>Serious Adverse Events</b>	1192 (7 RCTs) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>2,3,7</sup> due to risk of bias, imprecision	<b>Relative Risk 0.95</b> (0.76 to 1.18)	<b>213 per 1000</b>	<b>11 fewer per 1000</b> (from 51 fewer to 38 more)
<b>Total Adverse Events</b>	848 (6 RCTs) 12 months	⊕⊕⊕⊕ <b>MODERATE</b> <sup>7</sup> due to risk of bias	<b>Relative Risk 0.97</b> (0.9 to 1.05)	<b>753 per 1000</b>	<b>23 fewer per 1000</b> (from 75 fewer to 38 more)
<b>Upper GI Adverse Events</b>	996 (4 RCTs) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>7</sup> due to risk of bias	<b>Relative Risk 1.14</b> (0.88 to 1.48)	<b>184 per 1000</b>	<b>26 more per 1000</b> (from 22 fewer to 88 more)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness

**TABLE 41. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION ORAL BISPHOSPHONATE < AGE 40 WITHOUT PAST FRAGILITY FRACTURE AND WITHOUT BMD Z SCORE < -3**

<b>Outcomes</b>	<b>No of Participants (studies) Follow up</b>	<b>Certainty of the evidence (GRADE)</b>	<b>Relative effect (95% CI)</b>	<b>Anticipated absolute effects</b>	
				<b>Risk with Calcium and Vitamin D alone*</b>	<b>Risk difference with Oral Bisphosphonate (95% CI)**</b>

<b>Hip Fracture</b>	21,811 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.71</b> (0.55 to 0.91)	<b>19 per 1000</b> Over a mean of 2.5 years	<b>6 fewer per 1000</b> (from 2 fewer to 8 fewer)
<b>Vertebral Fracture</b>	10,500 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.59</b> (0.51 to 0.68)	<b>88 per 1000</b> Over a mean of 2.5 years	<b>36 fewer per 1000</b> (from 28 fewer to 43 fewer)
<b>Non-Vertebral Fracture</b>	22,022 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.84</b> (0.77 to 0.91)	<b>106 per 1000</b> Over a mean of 2.5 years	<b>17 fewer per 1000</b> (from 10 fewer to 24 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Cochrane Database Syst Rev. 2008 Jan 23; \(1\):CD001155](#).<sup>[21]</sup>; [Cochrane Database Syst Rev. 2008 Jan 23; \(1\):CD004523](#) <sup>[22]</sup>

<sup>1</sup> 4/5 studies were rated "high risk of bias" in at least one category. 3 studies were "high risk of bias" in at least 2 categories

<sup>2</sup> 3 studies had effects with wide 95% CI.

<sup>3</sup> The effect of at least one study is inestimable due to zero events

<sup>4</sup> Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

<sup>5</sup> Outcome is only assessed by one study

<sup>6</sup> 2/7 studies are open label. More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>7</sup> More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>8</sup> 4 studies have very wide 95% CI

#### 4.5.a. IV bisphosphonate vs CA/Vit D

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 42. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION IV BISPHOSPHONATE < AGE 40 WITHOUT PAST FRAGILITY FRACTURE AND WITHOUT BMD Z SCORE < -3**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with IV Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.70</b> (0.42 to 1.17)	<b>23 per 1000</b> Over 3 years	<b>7 fewer per 1000</b> (from 13 fewer to 4 more)
<b>Vertebral Fracture</b>	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.57</b> (0.35 to 0.91)	<b>109 per 1000</b> Over 3 years	<b>47 fewer per 1000</b> (from 10 fewer to 71 fewer)
<b>Non-Vertebral Fracture</b>	2,127 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.74</b> (0.56 to 0.94)	<b>100 per 1000</b> Over 3 years	<b>26 fewer per 1000</b> (from 6 fewer to 44 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 209](#) <sup>[23]</sup>; [Lyles, et al., N Engl J Med. 2007; 357\(18\):1799-809](#) <sup>[24]</sup>.

The **assumed risk**\* is based on the number of events in the control arms across studies. The **corresponding risk**\*\* (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

#### 4.6.a. Teriparatide vs Ca/Vit D

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 43. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION TERIPARATIDE < AGE 40 WITHOUT PAST FRAGILITY FRACTURE AND WITHOUT BMD Z SCORE < -3**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Teriparatide (95% CI)**
<b>Hip Fracture</b>	1,637 (1 RCT) 2 years	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2</sup>	<b>Relative Risk 0.50</b> (0.09 to 2.73)	<b>7 per 1000</b> Over 2 years	<b>4 fewer per 1000</b> (from 6 fewer to 12 more)
<b>Vertebral Fracture</b>	4,359 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.36</b> (0.28 to 0.47)	<b>143 per 1000</b> Over 2 years	<b>92 fewer per 1000</b> (from 76 fewer to 103 fewer)
<b>Non-Vertebral Fracture</b>	2,377 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.62</b> (0.48 to 0.82)	<b>97 per 1000</b> Over 2 years	<b>37 fewer per 1000</b> (from 18 fewer to 50 fewer)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209 \[23\]](#); [Neer, et al., N Engl J Med. 2001 May 10; 344\(19\):1434-41 \[29\]](#); [Stevenson, et al. Health Technol Assess. 2005 Jun;9\(22\):1-160 \[30\]](#); [Vestergaard, et al. Osteoporos Int. 2007 Jan;18\(1\):45-57 \[31\]](#)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio.

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Wide 95% confidence intervals

#### **4.7.a. Denosumab vs Ca/Vit D**

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.



- Certainty of evidence across all critical outcomes for GIOP population: Very low

**TABLE 44. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION DENOSUMAB < AGE 40 WITHOUT PAST FRAGILITY FRACTURE AND WITHOUT BMD Z SCORE < -3**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Denosumab (95% CI)**
<b>Hip Fracture</b>	7,297 (1 RCT) 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk 0.59</b> (0.36 to 0.94)	<b>11 per 1000</b> Over 3 years	<b>5 fewer per 1000</b> (from 1 fewer to 7 fewer)
<b>Vertebral Fracture</b>	7,738 (2 RCTs) 2 to 3 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 0.32</b> (0.25 to 0.41)	<b>72 per 1000</b> Over 3 years	<b>49 fewer per 1000</b> (from 43 fewer to 54 fewer)
<b>Non-Vertebral Fracture</b>	7,657 (2 RCTs) 2 to 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>2</sup> due to imprecision	<b>Relative Risk 0.65</b> (0.28 to 1.51)	<b>75 per 1000</b> Over 3 years	<b>26 fewer per 1000</b> (from 54 fewer to 38 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012;](#) [Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 12: 209;](#)<sup>[23]</sup> [Bone, et al. J Clin Endocrinol Metab. 2008; 93 \(6\):2149-57](#) <sup>[32]</sup>; [Cummings, et al. N Engl J Med. 2009 Aug 20; 361 \(8\):756-65](#) <sup>[33]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; .

<sup>1</sup> Outcome is only assessed by one study

<sup>2</sup> 95% CI of one trial passes beyond the other and passes null effect

#### **4.8.a. IV bisphosphonate vs Oral bisphosphonate**

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

- Certainty of evidence across all critical outcomes for GIOP population: Low

**TABLE 45. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR IV BISPHOSPHONATE FOR ADULTS < AGE 40 WITHOUT PAST FRAGILITY FRACTURE AND WITHOUT BMD Z SCORE < -3**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture	833 (1 RCT)	⊕⊕⊕⊖ LOW <sup>1,2,3</sup> due to imprecision	Relative Risk 1.67 (0.4 to 6.95)	7 per 1000	5 more per 1000 (from 4 fewer to 43 more)
12 months	12 months				
Non-Vertebral Fracture					
			No data		
Serious Adverse Events	833 (1 RCT) 12 months	⊕⊕⊕⊖ LOW <sup>1,3</sup> due to imprecision	Relative Risk 0.99 (0.74 to 1.32)	185 per 1000	2 fewer per 1000 (from 48 fewer to 59 more)
Total Adverse Events	833 (1 RCT) 12 months	⊕⊕⊕⊖ LOW <sup>1,3</sup> due to imprecision	Relative Risk 1.16 (1.06 to 1.26)	669 per 1000	107 more per 1000 (from 40 more to 174 more)
Bibliography: <a href="#">Reid, et al. Lancet. 2009 Apr 11; 373(9671): 1253-63</a> <sup>[34]</sup>					
The <b>assumed risk*</b> is based on the number of events in the control arms across studies. The <b>corresponding risk**</b> (and its 95% confidence interval) is based on the assumed risk and the <b>relative effect</b> of the intervention (and its 95% CI).					
CI: Confidence interval; RR: Risk ratio;					

**TABLE 46. EVIDENCE AVAILABLE FOR IV BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**

Hip Fracture			No data		
Vertebral Fracture	131 (2 RCTs) 1 year	⊕⊖⊖⊖ VERY LOW	Relative Risk 1.50 (0.29 to 7.73)	31 per 1000 Over 1 year	15 more per 1000 (from 22 fewer to 207 more)
Non-Vertebral Fracture			No data		
Bibliography: <a href="#">Crandall, et al. AHRQ CER 53, March 2012</a> ; <a href="#">Tauchmanová, et al. Bone Marrow Transplant. 2006 Jan; 37 (1):81-8 [35]</a> ; <a href="#">Chávez-Valencia, et al. J Clin Densitom. 2014 Oct-Dec;17(4):484-9 [36]</a>					

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> 95% CI is wide and crosses null effect

<sup>3</sup> Per Panel Request, Reid 2009 was downgraded from an original grade of “Moderate” to a new grade of “Low” (5/14/16)

#### 4.9.a. Teriparatide vs Oral bisphosphonate

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 47. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR TERIPARATIDE VS ORAL BISPHOSPHONATE ADULTS < AGE 40 WITHOUT PAST FRAGILITY FRACTURE OR AND WITHOUT BMD Z SCORE < -3**

**Bibliography:** [Saag, et al. N Engl J Med. 2007 Nov 15; 357\(20\): 2028-39 \[38\]](#); [Saag, et al. Arthritis Rheum. 2009 Nov; 60\(11\): 3346-55 \[39\]](#)

<b>Outcomes</b>	<b>No of Participants (studies) Follow up</b>	<b>Certainty of the evidence (GRADE)</b>	<b>Relative effect (95% CI)</b>	<b>Anticipated absolute effects</b>	
				<b>Risk with Oral Bisphosphonate *</b>	<b>Risk difference with Teriparatide (95% CI)**</b>
<b>Hip Fracture</b>	428 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3,5</sup>	<b>Relative Risk 0.33</b> (0.01 to 8.14)	<b>5 per 1000</b>	<b>3 fewer per 1000</b> (from 5 fewer to 33 more)
<b>18 months</b>	18 months	due to risk of bias, imprecision			

<b>Vertebral Fracture</b>	342 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk</b> <b>0.23</b> (0.07 to 0.78)	<b>77 per 1000</b>	<b>59 fewer per 1000</b> (from 17 fewer to 72 fewer)
<b>36 months</b>	36 months	due to imprecision			
<b>Vertebral Fracture</b>	336 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,5</sup>	<b>Relative Risk</b> <b>0.1</b> (0.01 to 0.75)	<b>61 per 1000</b>	<b>55 fewer per 1000</b> (from 15 fewer to 60 fewer)
<b>18 months</b>	18 months	due to imprecision			
<b>Non-Vertebral Fracture</b>	428 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk</b> <b>1.07</b> (0.54 to 2.1)	<b>70 per 1000</b>	<b>5 more per 1000</b> (from 32 fewer to 77 more)
<b>36 months</b>	36 months	due to risk of bias, imprecision			
<b>Non-Vertebral Fracture</b>	428 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3,5</sup>	<b>Relative Risk</b> <b>1.5</b> (0.63 to 3.6)	<b>37 per 1000</b>	<b>19 more per 1000</b> (from 14 fewer to 97 more)
<b>18 months</b>	18 months	due to imprecision			
<b>Serious Adverse Events</b>	428 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk</b> <b>1.06</b> (0.87 to 1.28)	<b>299 per 1000</b>	<b>18 more per 1000</b> (from 39 fewer to 84 more)
	36 months	due to imprecision			
<b>Total Adverse Events</b>	428 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk</b> <b>1.05</b> (0.98 to 1.13)	<b>860 per 1000</b>	<b>43 more per 1000</b> (from 17 fewer to 112 more)
	36 months	due to imprecision			

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> 31% discontinuation rate at 18 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> 95% CI is wide

<sup>4</sup> 44% discontinuation rate at 36 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>5</sup> Per Panel Request, Saag 2007 and Saag 2009 were downgraded from an original grade of “Moderate” to a new grade of “Low” due to small sample size and incredible treatment effects (5/14/16)

**TABLE 48. EVIDENCE AVAILABLE FOR TERIPARATIDE GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with Oral Bisphosphonate*		Risk difference with Teriparatide (95% CI)**
Hip Fracture				No data		
Vertebral Fracture				No data		
Non-Vertebral Fracture	146 (1 RCT) 1 year	⊕⊕⊖⊖ LOW <sup>2,4,5</sup>	Relative Risk 0.30 (0.09 to 1.05)	137 per 1000 1 year	Over	96 fewer per 1000 (from 125 fewer to 7 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Body, et al. J Clin Endocrinol Metab. 2002 Oct;87\(10\):4528-35](#) <sup>[40]</sup>

<sup>1</sup> 31% discontinuation rate at 18 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> 95% CI is wide

<sup>4</sup> 44% discontinuation rate at 36 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>5</sup> Per Panel Request, Saag 2007 and Saag 2009 were downgraded from an original grade of “Moderate” to a new grade of “Low” due to small sample size and incredible treatment effects (5/14/16)

#### 4.10.a. Denosumab vs Oral bisphosphonate

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 4.11.a. Teriparatide vs IV bisphosphonate

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **4.12.a. Denosumab vs IV bisphosphonate**

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **4.13.a. Denosumab vs Teriparatide**

In adults < age 40 without past fragility fracture or and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with teriparatide calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### ***V. MEN AND WOMEN (NOT OF CHILDBEARING POTENTIAL) UNDER 40 WITH NEITHER BMD Z SCORE < -3 AT HIP OR SPINE NOR ANY PAST FRAGILITY FRACTURE BUT WITH RAPID DECLINE IN BONE MASS TREATMENT QUESTIONS***

#### **4.1b. Oral bis vs Ca/Vit D**

In adults < age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a rapid decline in spine and/or hip BMD OF 10% while taking glucocorticoid therapy, what are the benefits and harms of oral bisphosphonates, calcium and vitamin D versus calcium and vitamin D alone?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **4.2b. IV bis vs CA/Vit D**

In adults <age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a rapid decline in spine and/or hip BMD OF 10% while taking glucocorticoid therapy, what are the benefits and harms of IV bisphosphonates, calcium and vitamin D versus calcium and vitamin D alone?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **4.3b. IV bis vs Oral bisphosphonate**

In adults <age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a rapid decline in spine and/or hip BMD OF 10% while taking glucocorticoid therapy, what are the benefits and harms of IV bisphosphonate, calcium and vitamin D versus oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **4.4.b. Teriparatide vs Ca/Vit D**

In adults <age 40, with closed growth plates, with neither prior fracture nor BMD Z score < -3 at hip or spine but with a rapid decline in spine and/or hip BMD OF 10% while taking glucocorticoid therapy, what are the benefits and harms of teriparatide, calcium and vitamin D versus calcium and vitamin D alone?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **4.5.b. Denosumab vs Ca/Vit D**

In adults <age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a rapid decline in spine and/or hip BMD OF 10% while taking glucocorticoid therapy, what are the benefits and harms of denosumab, calcium and vitamin D versus calcium and vitamin D alone?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## VI. ADULTS WITH ORGAN TRANSPLANT TREATMENT QUESTIONS

### 5.1. Vit D+Ca vs Placebo

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population:** Very low

**TABLE 49. SUMMARY OF FINDINGS FOR GIOP POPULATION CALCIUM/VIT D FOR RENAL TRANSPLANT RECIPIENTS ON GLUCOCORTICOIDS**

**Bibliography:** [Talalaj, et al. Transplant Proc. 1996 Dec; 28\(6\):3485-7 \[7\]](#); [Cueto-Manzano, et al. Am J Kidney Dis. 2000 Feb; 35\(2\):227-36<sup>+</sup> \[8\]](#); [De Sévaux, et al. J Am Soc Nephrol. 2002 Jun; 13\(6\):1608-14 \[9\]](#); [Josephson, et al. Transplantation. 2004 Oct 27;78\(8\):1233-6<sup>+</sup> \[10\]](#)

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium & Vitamin D Supplementation (95% CI)**
Hip Fracture			No data		
Vertebral Fracture 6 months	111 (1 RCT) 6 months	⊕⊕⊕⊕ VERY LOW <sup>1,2,3,4,5</sup> due to risk of bias, indirectness, imprecision	Relative Risk 0.14 (0.01 to 2.9)	43 per 1000	37 fewer per 1000 (from 43 fewer to 83 more)
Vertebral Fracture 12 months	30 (1 RCT) 12 months	⊕⊕⊕⊕ VERY LOW <sup>1,3,5,6</sup> due to risk of bias, imprecision	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	
Non-Vertebral Fracture 12 months	107 (2 RCTs) 12 months	⊕⊕⊕⊕ VERY LOW <sup>1,3,6</sup> due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months	



<b>Hypercalcaemia</b> <b>6 months</b>	111 (1 RCT) 6 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4,5</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk 2.12</b> (0.45 to 10.05)	<b>43 per 1000</b>	<b>49 more per 1000</b> (from 24 fewer to 393 more)
<b>Hypercalcaemia</b> <b>12 months</b>	51 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>3,4,5,7</sup> due to risk of bias, imprecision	<b>Relative Risk 3.85</b> (0.9 to 16.38)	<b>80 per 1000</b>	<b>228 more per 1000</b> (from 8 fewer to 1000 more)
<b>Transplant Rejection</b>	111 (1 RCT) 6 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,5</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk 0.97</b> (0.49 to 1.91)	<b>239 per 1000</b>	<b>7 fewer per 1000</b> (from 122 fewer to 218 more)
<b>Death</b>	111 (1 RCT) 6 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,5,6</sup> due to risk of bias, indirectness, imprecision	Not estimable	No incidence of Death in either group over 6 months	

<sup>1</sup> Open label trial(s)

<sup>2</sup> Outcomes assessed at time points <1 year were agreed to be indirect

<sup>3</sup> Small sample size

<sup>4</sup> 95% CI is (are) wide

<sup>5</sup> Outcome only assessed by one study

<sup>6</sup> Due to zero events, effect of at least one trial is inestimable

<sup>7</sup> Over 20% discontinuation in one or both groups

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients in Cueto-Manzano, et al., 2000 and Josephson, et al., 2004 were taking Calcitriol, an active form of Vitamin D

CI: Confidence interval; RR: Risk ratio;

**Table 50. EVIDENCE FOR CALCIUM/VIT D GENERAL OSTEOPOROSIS POPULATION WITH RENAL TRANSPLANT**

**Bibliography:** Crandall, et al. AHRQ CER 53, March 2012; Grant, et al., Lancet. 2005 May 7-13; 365 (9471):1621-8 [3]; Porthouse, et al. BMJ.

2005; 330(7498):1003 [4]; Jackson, et al. N Engl J Med. 2006;354(7):669-83 [5]; Salovaara, et al. J Bone Miner Res. 2010 Jul;25 (7):1487-95 [6]

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Supplementation*	Risk difference with Calcium & Vitamin D Supplementation (95% CI)**
<b>Hip Fracture</b>	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.98</b> (0.77 to 1.25)	<b>11 per 1000</b> Over a mean of 4.5 years	<b>0 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Vertebral Fracture</b>	42,115 (3 RCTs) 3 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.90</b> (0.74 to 1.09)	<b>10 per 1000</b> Over a mean of 5 years	<b>1 fewer per 1000</b> (from 3 fewer to 1 more)
<b>Non-Vertebral Fracture</b>	5,833 (2 RCTs) 3 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.93</b> (0.78 to 1.09)	<b>88 per 1000</b> Over a mean of 5 years	<b>6 fewer per 1000</b> (from 19 fewer to 8 more)

<sup>1</sup> 95% CI is (are) wide

## 5.2. Lifestyle vs Ca/Vit D

For adults with organ transplants (and GFR<sub>≥</sub> 30 and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## 5.3. Lifestyle+CA/D vs Ca/Vit D

For adults with organ transplants (and GFR<sub>≥</sub> 30 and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 5.4. Oral bisphosphonate vs CA/Vit D

For adults with organ transplants (and GFR $\geq$ 30 and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 51. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATE FOR RENAL TRANSPLANTS ON GLUCOCORTICOIDS**

**Bibliography:** [Atamaz†, et al. Osteoporos Int. 2006; 17\(6\): 942-9 \[41\]](#); [Guadalix, et al. Transpl Int. 2011 Jul; 24\(7\): 657-65 \[42\]](#)

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D and Calcium alone*	Risk difference with Oral Bisphosphonate (95% CI)*
Hip Fracture			No data		
Vertebral fracture	92 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2,3</sup> due to risk of bias, imprecision	Relative Risk 0.47 (0.13 to 1.7)	146 per 1000	77 fewer per 1000 (from 127 fewer to 102 more)
24 months	24 months				
Vertebral fracture	181 (2 RCTs)	⊕⊕⊖⊖ LOW <sup>1,3,4</sup> due to risk of bias, imprecision	Relative Risk 0.43 (0.16 to 1.17)	130 per 1000	74 fewer per 1000 (from 110 fewer to 22 more)
12 months	12 months				
Non-Vertebral Fracture	92 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2,3,4</sup> due to risk of bias, imprecision	Relative Risk 0.22 (0.01 to 4.41)	42 per 1000	33 fewer per 1000 (from 41 fewer to 142 more)
24 months	24 months				
Non-Vertebral	181 (2 RCTs)	⊕⊕⊖⊖ LOW <sup>1,3,4,5</sup>	Relative Risk 0.36	11 per 1000	7 fewer per 1000 (from 11 fewer to 83 more)

<b>Fracture</b>	12 months	due to risk of bias, imprecision	(0.02 to 8.68)		
<b>12 months</b>					
<b>Death</b>	187 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,3,4</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>1.97</b> (0.51 to 7.61)	<b>32 per 1000</b>	<b>31 more per 1000</b> (from 16 fewer to 213 more)
<b>Transplant Rejection</b>	89 (1 RCT) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>0.61</b> (0.31 to 1.2)	<b>364 per 1000</b>	<b>142 fewer per 1000</b> (from 251 fewer to 73 more)
<b>GI Adverse Events</b>	89 (1 RCT) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>2.61</b> (0.74 to 9.19)	<b>68 per 1000</b>	<b>110 more per 1000</b> (from 18 fewer to 558 more)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†All patients in Atamaz, et al. received Calcitriol, an active form of Vitamin D

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Open label trial(s)

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> Small sample size

<sup>4</sup> 95% CI of at least one study is wide

<sup>5</sup> Due to zero events, effect of one trial is inestimable

**TABLE 52. EVIDENCE AVAILABLE FOR ORAL BISPHOSPHONATE IN RENAL TRANSPLANT RECIPIENTS IN GENERAL POPULATION**

**Bibliography:** [Giannini, et al. J Bone Miner Res. 2001 Nov; 16\(11\): 2111-7<sup>†</sup> \[43\]](#); [Torregrosa, et al. Transpl Int. 2007 Aug; 20\(8\): 708-1; Trabulus, et al. Transplant Proc. 2008 Jan-Feb;40\(1\):160-6 \[44\]](#); [Torregrosa, et al. Transplantation. 2010 Jun 27; 89\(12\): 1476-81 \[45\]](#); [Coco, et al. J Am Soc Nephrol. 2012 Aug;23\(8\):1426-37<sup>†</sup> \[46\]](#)

Outcomes	No of Participants	Certainty of the	Relative effect	Anticipated absolute effects
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	(studies) Follow up	evidence (GRADE)	(95% CI)	Risk with Calcium and Vitamin D alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	164 (3 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	Not estimable	No incidence of Hip Fracture in either group over 12 months. Effect not estimable.	
<b>12 months</b>	12 months				
<b>Vertebral Fracture</b>	245 (4 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>0.72</b> (0.29 to 1.82)	<b>79 per 1000</b>	<b>22 fewer per 1000</b> (from 56 fewer to 65 more)
<b>12 months</b>	12 months				
<b>Non-Vertebral Fracture</b>	119 (2 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months. Effect not estimable.	
<b>12 months</b>	12 months				
<b>Total Adverse Events</b>	101 (1 RCT) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>0.77</b> (0.47 to 1.25)	<b>449 per 1000</b>	<b>103 fewer per 1000</b> (from 238 fewer to 112 more)
<b>Gastrointestinal Adverse Events</b>	40 (1 RCT) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>1</b> (0.29 to 3.45)	<b>200 per 1000</b>	<b>0 fewer per 1000</b> (from 142 fewer to 490 more)
<b>Transplant Rejection</b>	223 (3 RCTs) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3,5</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>1.26</b> (0.3 to 5.33)	<b>26 per 1000</b>	<b>7 more per 1000</b> (from 18 fewer to 113 more)
<b>Death</b>	185 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3,5</sup> due to risk of bias,	<b>Relative Risk</b> <b>0.31</b> (0.01 to 7.54)	<b>11 per 1000</b>	<b>7 fewer per 1000</b> (from 11 fewer to 70 more)

## imprecision

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients in Giannini et al, 2001 and Coco et al, 2012 received Calcitriol, an active form of Vitamin D. ‡Patients in Trabulus et al, 2008 received Alfacalcidol, an active form of Vitamin D.

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness

PICO 5.5: For adults with organ transplants (and GFR ≥ 30 mL/min and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 53. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR IV BISPHOSPHONATE IN RENAL TRANSPLANT ON GLUCOCORTICOID**

**Bibliography:** [Crawford, et al. Ann Intern Med. 2006 Feb 21; 144\(4\):239-48 \[47\]](#); [Bodingbauer, et al. Am J Transplant. 2007 Jul; 7\(7\): 1763-9 \[48\]](#); [Fahrleitner-Pammer, et al. J Bone Miner Res. 2009 Jul; 24\(7\): 1335-44 \[49\]](#); [Kaemmerer, et al. Transpl Int. 2010 Jul; 23\(7\): 753-9 \[50\]](#)

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with IV Bisphosphonate (95% CI)**
<b>Hip Fracture</b>			No data		
<b>Vertebral Fracture</b>	154 (2 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2</sup>	<b>Relative Risk</b> <b>0.36</b>	<b>188 per 1000</b>	<b>120 fewer per 1000</b> (from 13 fewer to 161)

<b>24 months</b>	24 months	due to risk of bias, (0.14 to 0.93) imprecision			fewer)
<b>Vertebral Fracture</b>	94 (2 RCTs)	⊕⊕⊕⊕ <b>LOW</b> <sup>2,3</sup>	<b>Relative Risk</b> <b>0.24</b>	<b>234 per 1000</b>	<b>178 fewer per 1000</b> (from 40 fewer to 218 fewer)
<b>12 months</b>	12 months	due to risk of bias, (0.07 to 0.83) imprecision			
<b>Non-Vertebral Fracture</b>	58 (1 RCT)	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>4,5,6</sup>	<b>Relative Risk</b> <b>0.29</b>	<b>129 per 1000</b>	<b>92 fewer per 1000</b> (from 125 fewer to 182 more)
<b>24 months</b>	24 years	due to risk of bias, (0.03 to 2.41) imprecision			
<b>Non-Vertebral Fracture</b>	62 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>2,3</sup>	<b>Relative Risk</b> <b>1.88</b>	<b>33 per 1000</b>	<b>29 more per 1000</b> (from 27 fewer to 621 more)
<b>12 months</b>	12 months	due to risk of bias, (0.18 to 19.63) imprecision			
<b>Transplant Rejection</b>	96 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>5,6,7</sup>	<b>Relative Risk</b> <b>1.46</b>	<b>122 per 1000</b>	<b>56 more per 1000</b> (from 45 fewer to 239 more)
	24 months	due to risk of bias, (0.63 to 2.95) imprecision			
<b>Hypocalcaemia</b>	96 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>5,6,7</sup>	<b>Relative Risk</b> <b>3.65</b>	<b>41 per 1000</b>	<b>108 more per 1000</b> (from 8 fewer to 640 more)
<b>24 months</b>	24 months	due to risk of bias, (0.8 to 16.68) imprecision			
<b>Hypocalcaemia</b>	62 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>5,6,7</sup>	<b>Relative Risk</b> <b>4.06</b>	<b>100 per 1000</b>	<b>306 more per 1000</b> (from 28 more to 1000 more)
<b>12 months</b>	12 months	due to risk of bias, (1.28 to 12.86) imprecision			

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> OPEN LABEL trials. One of the studies assessing this outcome was rated "high risk of bias" in 5/7 categories; the other study was rated "high risk of bias" in 2/7 categories.

<sup>2</sup> Both trials have small sample size. 95% CI of one trial is wide and crosses null effect.

<sup>3</sup> Inconsistencies in reporting in one of the included trials.

<sup>4</sup> OPEN LABEL trial. Rated "high risk of bias" in 5/7 categories. Evidence of differential baseline characteristics between groups.

<sup>5</sup> Outcome only assessed by one study

<sup>6</sup> 95% CI is wide; very small sample size

<sup>7</sup> OPEN label trial

**TABLE 54. EVIDENCE AVAILABLE FOR IV BISPHOSPHONATE IN RENAL TRANSPLANT RECIPIENTS IN GENERAL POPULATION**

**Bibliography:** [Smerud, et al. Am J Transplant. 2012 Dec;12\(12\): 3316-25](#) † <sup>[51]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with IV Bisphosphonate (95% CI)*
Hip Fracture			No data		
Vertebral Fracture	129 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2,3</sup>	Relative Risk 1.91	16 per 1000	14 more per 1000
12 months	12 months	due to imprecision	(0.17 to 16.42)		(from 13 fewer to 245 more)
Non-Vertebral Fracture			No data		
Serious Adverse Events	129 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>	Relative Risk 0.57	587 per 1000	253 fewer per 1000
	12 months	due to imprecision	(0.33 to 0.86)		(from 82 fewer to 393 fewer)
Total Adverse Events	129 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>	Relative Risk 0.83	937 per 1000	159 fewer per 1000
	12 months	due to imprecision	(0.54 to 0.98)		(from 19 fewer to 431 fewer)
Transplant Rejection	129 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>	Relative Risk 0.78	349 per 1000	77 fewer per 1000
	12 months	due to imprecision	(0.43 to 1.27)		(from 199 fewer to 94 more)

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> Very small sample size

<sup>3</sup> 95% CI is very wide



### 5.6. Teriparatide vs Ca/Vit D

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 5.7. Abaloparatide vs CA.VITD

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 5.8. Denosumab vs Ca/Vit D

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 5.9. Romosozumab vs ca/vit D

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 5.10. Active Vit D plus Ca vs Ca/Vit D

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with active forms of vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 5.11. IV bisphosphonate vs Oral bisphosphonate

For adults with organ transplants (and  $GFR \geq 35$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 55. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR IV BISPHOSPHONATES IN RENAL TRANSPLANTS ON GLUCOCORTICOIDS**

Evidence Available:

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture 12 months	69 (1 RCT) 12 months	⊕⊕⊖⊖ LOW <sup>1,2,3</sup> due to imprecision	RR 0.22 (0.01 to 4.37)	56 per 1000	43 fewer per 1000 (from 55 fewer to 187 more)
Non-Vertebral Fracture 12 months	69 (1 RCT) 12 months	⊕⊕⊖⊖ LOW <sup>1,2,3</sup> due to imprecision	RR 0.36 (0.04 to 3.33)	83 per 1000	53 fewer per 1000 (from 80 fewer to 194 more)
Serious Adverse Events	84 (1 RCT) 12 months	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to imprecision	RR 1.57 (0.93 to 2.66)	326 per 1000	186 more per 1000 (from 23 fewer to 540 more)
Transplant Rejection	84 (1 RCT) 12 months	⊕⊕⊖⊖ LOW <sup>1,2,3</sup> due to imprecision	RR 2.1 (0.41 to 10.84)	47 per 1000	51 more per 1000 (from 27 fewer to 458 more)
Hypocalcaemia	84 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,3</sup>	RR 0.84 (0.24 to 2.91)	116 per 1000	19 fewer per 1000 (from 88 fewer to 222 more)

12 months	due to imprecision	
<b>Bibliography:</b> Shane, et al. J Clin Endocrinol Metab. 2012 Dec; 97(12): 4481-90 <sup>[52]</sup> The <b>assumed risk*</b> is based on the number of events in the control arms across studies. The <b>corresponding risk**</b> (and its 95% confidence interval) is based on the assumed risk and the <b>relative effect</b> of the intervention (and its 95% CI). <b>CI:</b> Confidence interval; <b>RR:</b> Risk ratio <sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome. <sup>2</sup> Outcome is only addressed by one study <sup>3</sup> Very small sample size at the time point measured. <sup>4</sup> Received "high risk of bias" rating in 5/7 categories. <sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness		

### 5.12. Teriparatide vs Oral bisphosphonate

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 5.13 Abaloparatide vs oral bisphosphonate

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 5.14. Denosumab vs Oral bisphosphonate

For adults with organ transplants (and  $\text{GFR} \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.15. Raloxifene vs Oral bisphosphonate**

For post-menopausal women with organ transplants (and  $\text{GFR} \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D versus treatment with oral bisphosphonate calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.16 Romosozumab vs oral bisphosphonate**

For adults with organ transplants (and  $\text{GFR} \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.17. Teriparatide vs IV bisphosphonate**

For adults with organ transplants (and  $\text{GFR} \geq 35$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.18. Denosumab vs IV bisphosphonate**

For adults with organ transplants (and  $GFR \geq 35$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.19. Raloxifene vs IV bisphosphonate**

For post-menopausal women with organ transplants (and  $GFR \geq 35$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D versus treatment with IV *bisphosphonate* calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.20 Abaloparatide vs IV bisphosphonate**

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.21 Romosozumab vs oral bisphosphonate**

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.22. Oral bisphosphonates vs Activated Vit D/Ca**

For adults with organ transplants (and  $\text{GFR} \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with oral bisphosphonates, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.23. IV bisphosphonates vs Activated Vit D/Ca**

For adults with organ transplants (and  $\text{GFR} \geq 35$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with IV bisphosphonates, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.24. PTH analogs vs Activated Vit D/Ca**

For adults with organ transplants (and  $\text{GFR} \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with teriparatide/abaloparatide, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.25. Denosumab vs Activated Vit D/Ca**

For adults with organ transplants (and  $\text{GFR} \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **5.26. Den vs PTH analogs**

For adults with organ transplants (and  $GFR \geq 30$  and no evidence of metabolic bone disease) continuing chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with teriparatide/abaloparatide, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## VII. MEN AND POST-MENOPAUSAL WOMEN $\geq 40$ YEARS WITH BOTH HIGH CURRENT GC DOSE AND HIGH CUMULATIVE GC DOSE TREATMENT QUESTIONS

### 6.1.a. Vit D+Ca vs Placebo

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 56. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR CALCIUM/VITAMIN D IN ADULTS  $\geq 40$  WITH GIOP AND CURRENT AND CUMMULATIVE HIGH DOSE GLUCOCORTICOIDS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Supplementation*	Risk difference with Calcium and Vitamin D Supplementation (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture	62 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2,3</sup>	Relative Risk 0.6 (0.16 to 2.3)	161 per 1000	65 fewer per 1000 (from 135 fewer to 210 more)
36 months	36 months	due to risk of bias, imprecision			
Vertebral Fracture	14 (1 RCT)	⊕⊖⊖⊖ VERY LOW <sup>2,3,4,5</sup>	Relative Risk 3.0 (0.14 to 63.15)	0 per 1000	-
6 months	6 months	due to risk of bias, indirectness, imprecision			

<b>Non-Vertebral Fracture</b>	14 (1 RCT) 6 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>2,3,4,5</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk 0.33</b> (0.02 to 7.02)	<b>143 per 1000</b>	<b>96 fewer per 1000</b> (from 140 fewer to 860 more)
<b>6 months</b>					
<b>Serious Adverse Events</b>			No data		
<b>Total Adverse Events</b>			No data		

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

**Bibliography:** [Braun, et al. Clin Endocrinol \(Oxf\). 1983 Aug; 19\(2\): 265-73†; \[1\]](#) [Adachi, et al. J Rheumatol. 1996 Jun; 23\(6\): 995-1000 \[2\]](#)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients receiving Calcium and Vitamin D in the Braun, et al. study received 1α-(OH) D3 (Etalpa), an active form of Vitamin D.

CI: Confidence interval; RR: Risk ratio;

**TABLE 57. EVIDENCE FOR CALCIUM/VIT D GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Calcium and Vitamin D*	Risk difference with Calcium and Vitamin D (95% CI)**
<b>Hip Fracture</b>	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊕ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.98</b> (0.77 to 1.25)	<b>11 per 1000</b> Over a mean of 4.5 years	<b>0 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Vertebral Fracture</b>	42,115	⊕⊕⊕⊕	<b>Relative Risk 0.90</b>	<b>10 per 1000</b>	<b>1 fewer per 1000</b>



	(3 RCTs) 3 to 7 years	<b>MODERATE</b> <sup>1</sup>	(0.74 to 1.09)	Over a mean of 5 years	(from 3 fewer to 1 more)
<b>Non-Vertebral Fracture</b>	5,833 (2 RCTs) 3 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.93</b> (0.78 to 1.09)	<b>88 per 1000</b> Over a mean of 5 years	<b>6 fewer per 1000</b> (from 19 fewer to 8 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Grant, et al., Lancet. 2005 May 7-13; 365 \(9471\):1621-8](#) <sup>[3]</sup>; [Porthouse, et al. BMJ. 2005; 330\(7498\):1003](#) <sup>[4]</sup>; [Jackson, et al. N Engl J Med. 2006;354\(7\):669-83](#) <sup>[5]</sup>; [Salovaara, et al. J Bone Miner Res. 2010 Jul;25 \(7\):1487-95](#) <sup>[6]</sup>

<sup>1</sup> 95% CI is (are) wide

#### 6.2.a. lifestyle vs Ca/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 6.3.a. lifestyle+CA/D vs Ca/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with lifestyle modifications, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 6.4.a. Oral bis vs Ca/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low to Moderate (Moderate for Adverse Events)**

**TABLE 58. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATE IN ADULTS ≥ 40 WITH GIOP ON HIGH DOSE STEROID POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	72 (1 RCT) 18 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.33</b> (0.01 to 7.92)	<b>28 per 1000</b>	<b>19 fewer per 1000</b> (from 28 fewer to 192 more)
<b>Vertebral Fracture</b>	109 (2 RCTs) 18 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4,6</sup> due to risk of bias, imprecision	<b>Relative Risk 0.13</b> (0.01 to 2.25)	<b>71 per 1000</b>	<b>62 fewer per 1000</b> (from 71 fewer to 89 more)
<b>Non-Vertebral Fracture</b>	72 (1 RCT) 18 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.33</b> (0.01 to 7.92)	<b>28 per 1000</b>	<b>19 fewer per 1000</b> (from 28 fewer to 192 more)

**Bibliography:** [Okada, et al. J Rheumatol. 2008 Nov;35\(11\):2249-54](#) <sup>[16]</sup>; [Saadati, 2008](#) <sup>[17]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness

**TABLE 59. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR BISPHOSPHONATE IN ADULTS ≥ 40 WITH GIOP ON HIGH DOSE STEROIDS**

**Bibliography:** [Saag, 1998](#) <sup>[11]</sup>; [Wallach, 2000](#) <sup>[12]</sup>; [Adachi, 2001](#) <sup>[13]</sup>; [Lems, 2006](#) <sup>[14]</sup>; [Yamada, 2007](#) <sup>[15]</sup>; [Okada, 2008](#) <sup>[16]</sup>; [Saadati, 2008](#) <sup>[17]</sup>; [Stoch,](#)

[2009 \[18\]](#), [Tee, 2012 \[19\]](#), [Hakala, 2012 \[20\]](#)

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D and Calcium alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	532 (5 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3</sup>	<b>Relative Risk 0.57</b> (0.09 to 3.56)	<b>9 per 1000</b>	<b>4 fewer per 1000</b> (from 8 fewer to 22 more)
<b>12 months</b>	12 months	due to risk of bias, imprecision			
<b>Vertebral Fracture</b>	202 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>4,5</sup>	<b>Relative Risk 0.1</b> (0.01 to 0.9)	<b>68 per 1000</b>	<b>61 fewer per 1000</b> (from 7 fewer to 67 fewer)
<b>24 months</b>	24 months	due to risk of bias, imprecision			
<b>Vertebral Fracture</b>	1051 (7 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>2,3,6</sup>	<b>Relative Risk 0.66</b> (0.25 to 1.77)	<b>69 per 1000</b>	<b>23 fewer per 1000</b> (from 52 fewer to 53 more)
<b>12 months</b>	12 months	due to risk of bias, imprecision			
<b>Non-Vertebral Fracture</b>	208 (1 RCT)	⊕⊕⊕⊖ <b>LOW</b> <sup>4,5</sup>	<b>Relative Risk 0.55</b> (0.2 to 1.53)	<b>98 per 1000</b>	<b>44 fewer per 1000</b> (from 79 fewer to 52 more)
<b>24 months</b>	24 months	due to risk of bias, imprecision			
<b>Non-Vertebral Fracture</b>	1353 (7 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>3,7,8</sup>	<b>Relative Risk 0.89</b> (0.52 to 1.53)	<b>43 per 1000</b>	<b>5 fewer per 1000</b> (from 21 fewer to 23 more)
<b>12 months</b>	12 months	due to risk of bias, imprecision			
<b>Serious Adverse Events</b>	1192 (7 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>2,3,7</sup>	<b>Relative Risk 0.95</b> (0.76 to 1.18)	<b>213 per 1000</b>	<b>11 fewer per 1000</b> (from 51 fewer to 38 more)
	12 months	due to risk of bias, imprecision			
<b>Total Adverse Events</b>	848 (6 RCTs)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>7</sup>	<b>Relative Risk 0.97</b> (0.9 to 1.05)	<b>753 per 1000</b>	<b>23 fewer per 1000</b> (from 75 fewer to 38 more)
	12 months	due to risk of bias			
<b>Upper GI Adverse</b>	996	⊕⊕⊕⊖	<b>Relative Risk</b>	<b>184 per 1000</b>	<b>26 more per 1000</b>

<b>Events</b>	(4 RCTs) 12 months	<b>MODERATE</b> <sup>7</sup> due to risk of bias	<b>1.14</b> (0.88 to 1.48)	(from 22 fewer to 88 more)
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The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> 4/5 studies were rated "high risk of bias" in at least one category. 3 studies were "high risk of bias" in at least 2 categories

<sup>2</sup> 3 studies had effects with very wide 95% CI.

<sup>3</sup> The effect of at least one study is inestimable due to zero events

<sup>4</sup> Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

<sup>5</sup> Outcome is only assessed by one study

<sup>6</sup> Small sample size

<sup>7</sup> 2/8 studies are open label. More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>8</sup> More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>9</sup> 4 studies have very wide 95% CI

#### 6.5.a. IV bisphosphonate vs Ca/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 6.6.a. SERM vs CA/Vit D

For post-menopausal women receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.7.a. Teriparatide vs Ca/Vit D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.8a Abaloparatide vs CA/VIT D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.9a Romosozumab vs CA/VIT D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.10.a. Denosumab vs Ca/Vit D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 6.11.a. IV bisphosphonate vs Oral bisphosphonate

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 6.12.a.SERM vs Oral bisphosphonates

For post-menopausal women receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 60. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR SERM VS ORAL BISPHOSPHONATE FOR POST-MENOPAUSAL WOMEN ON HIGH DOES STEROIDS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Raloxifene (95% CI)**
Hip Fracture			No data		
Vertebral Fracture	107 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3,4</sup> due to imprecision	<b>Relative Risk 0.16</b> (0.01 to 2.96)	<b>54 per 1000</b>	<b>45 fewer per 1000</b> (from 53 fewer to 105 more)
Non-Vertebral Fracture			No data		
Serious Adverse			No data		

Events					
<b>Total Adverse Events</b>	114 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4</sup> due to imprecision	<b>Relative Risk 0.88</b> (0.47 to 1.62)	<b>281 per 1000</b>	<b>34 fewer per 1000</b> (from 149 fewer to 174 more)

**Bibliography:** [Mok, et al. Ann Rheum Dis. 2011 May; 70\(5\): 778-84](#) <sup>[25]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Noted uneven distribution of discontinuations; very low discontinuation rate overall.

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> 95% CI is wide

<sup>4</sup> Very small sample size

<sup>5</sup> Control event rates were not available

### 6.13.a. Teriparatide vs Oral bisphosphonate

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 61. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR TERIPARATIDE VS ORAL BISPHOSPHONATE IN ADULTS  $\geq 40$  WITH GIOP ON HIGH DOSE STEROIDS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
<b>Hip Fracture</b>	428 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3,5</sup>	<b>Relative Risk 0.33</b>	<b>5 per 1000</b>	<b>3 fewer per 1000</b>
<b>18 months</b>	18 months	due to risk of bias, imprecision	(0.01 to 8.14)		(from 5 fewer to 33 more)
<b>Vertebral Fracture</b>	342 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk 0.23</b>	<b>77 per 1000</b>	<b>59 fewer per 1000</b>
					(from 17 fewer to 72 fewer)

<b>36 months</b>	36 months	due to imprecision	(0.07 to 0.78)		
<b>Vertebral Fracture</b>	336 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,5</sup>	<b>Relative Risk 0.1</b> (0.01 to 0.75)	<b>61 per 1000</b>	<b>55 fewer per 1000</b> (from 15 fewer to 60 fewer)
<b>18 months</b>	18 months	due to imprecision			
<b>Non-Vertebral Fracture</b>	428 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk 1.07</b> (0.54 to 2.1)	<b>70 per 1000</b>	<b>5 more per 1000</b> (from 32 fewer to 77 more)
<b>36 months</b>	36 months	due to risk of bias, imprecision			
<b>Non-Vertebral Fracture</b>	428 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3,5</sup>	<b>Relative Risk 1.5</b> (0.63 to 3.6)	<b>37 per 1000</b>	<b>19 more per 1000</b> (from 14 fewer to 97 more)
<b>18 months</b>	18 months	due to imprecision			
<b>Serious Adverse Events</b>	428 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk 1.06</b> (0.87 to 1.28)	<b>299 per 1000</b>	<b>18 more per 1000</b> (from 39 fewer to 84 more)
	36 months	due to imprecision			
<b>Total Adverse Events</b>	428 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>2,4,5</sup>	<b>Relative Risk 1.05</b> (0.98 to 1.13)	<b>860 per 1000</b>	<b>43 more per 1000</b> (from 17 fewer to 112 more)
	36 months	due to imprecision			

**Bibliography:** [Saag, et al. N Engl J Med. 2007 Nov 15; 357\(20\): 2028-39](#) <sup>[38]</sup>. [Saag, et al. Arthritis Rheum. 2009 Nov; 60\(11\): 3346-55](#) <sup>[39]</sup>

<sup>1</sup> 31% discontinuation rate at 18 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> 95% CI is wide

<sup>4</sup> 44% discontinuation rate at 36 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>5</sup> Per Panel Request, Saag 2007 and Saag 2009 were downgraded from an original grade of “Moderate” to a new grade of “Low” due to small sample size and incredible treatment effects (5/14/16)

#### 6.14.a. Denosumab vs Oral bisphosphonate

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?



**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.15a Abaloparatide vs oral bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.16a Romosozumab vs oral bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.17.a. SERM vs IV bisphosphonate**

For post-menopausal women receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.18.a. Teri vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.19.a. Den vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.20a Abaloparatide vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.21a Romosozumab vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.22a. Teriparatide vs SERM**

For post-menopausal women receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with raloxifene, calcium, and vitamin D ?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.23a. Denosumab vs SERM**

For post-menopausal women receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with raloxifene, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.24a. Den vs Teriparatide**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with teriparatide, calcium, and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### ***VIII. MEN AND WOMEN (NOT OF CHILDBEARING POTENTIAL) UNDER 40 WITH BOTH HIGH CURRENT GC DOSE AND HIGH CUMULATIVE GC DOSE TREATMENT QUESTIONS***

#### **6.1.b. Vit D+Ca vs Placebo**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 62: SUMMARY OF FINDINGS FOR GIOP POPULATION FOR HIGH DOSE STEROID POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Calcium & Vitamin D	Risk difference with Calcium & Vitamin D Supplementation

				Supplementation* (95% CI)**	
<b>Hip Fracture</b>				No data	
<b>Vertebral Fracture</b>	62 (1 RCT)	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3</sup>	<b>Relative Risk 0.6</b> (0.16 to 2.3)	<b>161 per 1000</b>	<b>65 fewer per 1000</b> (from 135 fewer to 210 more)
<b>36 months</b>	36 months	due to risk of bias, imprecision			
<b>Vertebral Fracture</b>	14 (1 RCT)	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>2,3,4,5</sup>	<b>Relative Risk 3.0</b> (0.14 to 63.15)	<b>0 per 1000</b>	-
<b>6 months</b>	6 months	due to risk of bias, indirectness, imprecision			
<b>Non-Vertebral Fracture</b>	14 (1 RCT)	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>2,3,4,5</sup>	<b>Relative Risk 0.33</b> (0.02 to 7.02)	<b>143 per 1000</b>	<b>96 fewer per 1000</b> (from 140 fewer to 860 more)
<b>6 months</b>	6 months	due to risk of bias, indirectness, imprecision			
<b>Serious Adverse Events</b>				No data	
<b>Total Adverse Events</b>				No data	

**Bibliography:** [Braun, et al. Clin Endocrinol \(Oxf\). 1983 Aug; 19\(2\): 265-73†;](#)<sup>[1]</sup> [Adachi, et al. J Rheumatol. 1996 Jun;23\(6\): 995-1000](#)<sup>[2]</sup>

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

†Patients receiving Calcium and Vitamin D in the Braun, et al. study received 1α-(OH) D3 (Etalpha), an active form of Vitamin D.

**CI:** Confidence interval; **RR:** Risk ratio;

**TABLE 63. EVIDENCE FOR CALCIUM/VIT D IN GENERAL OSTEOPOROSIS POPULATION**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Calcium & Vitamin D Supplementation*	Risk difference with Calcium & Vitamin D Supplementation (95% CI)**
<b>Hip Fracture</b>	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.98</b> (0.77 to 1.25)	<b>11 per 1000</b> Over a mean of 4.5 years	<b>0 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Vertebral Fracture</b>	42,115 (3 RCTs) 3 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.90</b> (0.74 to 1.09)	<b>10 per 1000</b> Over a mean of 5 years	<b>1 fewer per 1000</b> (from 3 fewer to 1 more)
<b>Non-Vertebral Fracture</b>	5,833 (2 RCTs) 3 to 7 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup>	<b>Relative Risk 0.93</b> (0.78 to 1.09)	<b>88 per 1000</b> Over a mean of 5 years	<b>6 fewer per 1000</b> (from 19 fewer to 8 more)

**Bibliography:** [Crandall, et al. AHRQ CER 53, March 2012](#); [Grant, et al., Lancet. 2005 May 7-13; 365 \(9471\):1621-8 \[3\]](#); [Porthouse, et al. BMJ. 2005; 330\(7498\):1003 \[4\]](#); [Jackson, et al. N Engl J Med. 2006;354\(7\):669-83 \[5\]](#); [Salovaara, et al. J Bone Miner Res. 2010 Jul;25 \(7\):1487-95 \[6\]](#)

<sup>1</sup> 95% CI is (are) wide

### 6.2.b. lifestyle vs Ca/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 6.3.b. lifestyle+CA/D vs Ca/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with lifestyle modifications, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 6.4.b. Oral bis vs CA/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low to Moderate (Moderate for Adverse Events)**

**TABLE 64. EVIDENCE AVAILABLE FOR ADULTS <40 ON HIGH DOSE STEROIDS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	72 (1 RCT) 18 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.33</b> (0.01 to 7.92)	<b>28 per 1000</b>	<b>19 fewer per 1000</b> (from 28 fewer to 192 more)
<b>Vertebral Fracture</b>	109 (2 RCTs) 18 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4,6</sup> due to risk of bias, imprecision	<b>Relative Risk 0.13</b> (0.01 to 2.25)	<b>71 per 1000</b>	<b>62 fewer per 1000</b> (from 71 fewer to 89 more)
<b>Non-Vertebral Fracture</b>	72 (1 RCT) 18 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.33</b> (0.01 to 7.92)	<b>28 per 1000</b>	<b>19 fewer per 1000</b> (from 28 fewer to 192 more)

**Bibliography:** [Okada, et al. J Rheumatol. 2008 Nov;35\(11\):2249-54<sup>\[16\]</sup>](#); [Saadati, et al. Iranian Red Crescent Medical Journal 2008.1 \(2008\): 8-11<sup>\[17\]</sup>](#)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness

**TABLE 65. SUMMARY OF EVIDENCE FOR BISPHOSPHONATES IN ADULTS <40 WITH GIOP ON HIGH DOES STEROIDS**

**Bibliography:** [Saag, 1998](#) <sup>[11]</sup>; [Wallach, 2000](#) <sup>[12]</sup>; [Adachi, 2001](#) <sup>[13]</sup>; [Lems, 2006](#) <sup>[14]</sup>; [Yamada, 2007](#) <sup>[15]</sup>; [Okada, 2008](#) <sup>[16]</sup>; [Saadati, 2008](#) <sup>[17]</sup>; [Stoch, 2009](#) <sup>[18]</sup>; [Tee, 2012](#) <sup>[19]</sup>; [Hakala, 2012](#) <sup>[20]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Vitamin D and Calcium alone*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b> <b>12 months</b>	532 (5 RCTs) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>0.57</b> (0.09 to 3.56)	<b>9 per 1000</b>	<b>4 fewer per 1000</b> (from 8 fewer to 22 more)
<b>Vertebral Fracture</b> <b>24 months</b>	202 (1 RCT) 24 months	⊕⊕⊖⊖ <b>LOW</b> <sup>4,5</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>0.1</b> (0.01 to 0.9)	<b>68 per 1000</b>	<b>61 fewer per 1000</b> (from 7 fewer to 67 fewer)
<b>Vertebral Fracture</b> <b>12 months</b>	1051 (7 RCTs) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,3,6</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>0.66</b> (0.25 to 1.77)	<b>69 per 1000</b>	<b>23 fewer per 1000</b> (from 52 fewer to 53 more)
<b>Non-Vertebral Fracture</b>	208 (1 RCT)	⊕⊕⊖⊖ <b>LOW</b> <sup>4,5</sup>	<b>Relative Risk</b> <b>0.55</b>	<b>98 per 1000</b>	<b>44 fewer per 1000</b> (from 79 fewer to 52 more)

<b>24 months</b>	24 months	due to risk of bias, imprecision	(0.2 to 1.53)		
<b>Non-Vertebral Fracture</b>	1353 (7 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>3,7,8</sup>	<b>Relative Risk</b> <b>0.89</b> (0.52 to 1.53)	<b>43 per 1000</b>	<b>5 fewer per 1000</b> (from 21 fewer to 23 more)
<b>12 months</b>	12 months	due to risk of bias, imprecision			
<b>Serious Adverse Events</b>	1192 (7 RCTs)	⊕⊕⊕⊖ <b>LOW</b> <sup>2,3,7</sup>	<b>Relative Risk</b> <b>0.95</b> (0.76 to 1.18)	<b>213 per 1000</b>	<b>11 fewer per 1000</b> (from 51 fewer to 38 more)
	12 months	due to risk of bias, imprecision			
<b>Total Adverse Events</b>	848 (6 RCTs)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>7</sup>	<b>Relative Risk</b> <b>0.97</b> (0.9 to 1.05)	<b>753 per 1000</b>	<b>23 fewer per 1000</b> (from 75 fewer to 38 more)
	12 months	due to risk of bias			
<b>Upper GI Adverse Events</b>	996 (4 RCTs)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>7</sup>	<b>Relative Risk</b> <b>1.14</b> (0.88 to 1.48)	<b>184 per 1000</b>	<b>26 more per 1000</b> (from 22 fewer to 88 more)
	12 months	due to risk of bias			

<sup>1</sup> 4/5 studies were rated "high risk of bias" in at least one category. 3 studies were "high risk of bias" in at least 2 categories

<sup>2</sup> 3 studies had effects with very wide 95% CI.

<sup>3</sup> The effect of at least one study is inestimable due to zero events

<sup>4</sup> Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

<sup>5</sup> Outcome is only assessed by one study

<sup>6</sup> Small sample size

<sup>7</sup> 2/8 studies are open label. More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>8</sup> More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

<sup>9</sup> 4 studies have very wide 95% CI

#### 6.5.b. IV bisphosphonate vs Ca/Vit D

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?



**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.6.b. Teriparatide vs Ca/Vit D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.7.b. Denosumab vs Ca/Vit D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.8b Abaloparatide vs CA/VIT D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.9b Romosozumab vs CA/VIT D**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 6.10.b. IV bisphosphonate vs Oral bisphosphonate

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 66. SUMMARY FINDINGS FOR GIOP POPULATION FOR IV BISPHOSPHONATE VS ORAL BISPHOSPHONATE FOR ADULTS <40 WITH GIOP ON HIGH DOSE STEROIDS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with IV Bisphosphonate (95% CI)**
Hip Fracture					
			No data		
Vertebral Fracture	833 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2,3</sup> due to imprecision	Relative Risk 1.67 (0.4 to 6.95)	7 per 1000	5 more per 1000 (from 4 fewer to 43 more)
12 months	12 months				
Non-Vertebral Fracture					
			No data		
Serious Adverse Events	833 (1 RCT) 12 months	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to imprecision	Relative Risk 0.99 (0.74 to 1.32)	185 per 1000	2 fewer per 1000 (from 48 fewer to 59 more)
Total Adverse Events	833 (1 RCT) 12 months	⊕⊕⊖⊖ LOW <sup>1,3</sup> due to imprecision	Relative Risk 1.16 (1.06 to 1.26)	669 per 1000	107 more per 1000 (from 40 more to 174 more)

**Bibliography:** [Reid, et al. Lancet. 2009 Apr 11; 373\(9671\): 1253-63](#) <sup>[34]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence

interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Study received "high risk of bias" rating in 2/7 categories. High dropout rate and only approximately 30% of patients remained at the time point measured for this outcome.

<sup>2</sup> Outcome is only addressed by one study

<sup>3</sup> Very small sample size at the time point measured.

<sup>4</sup> Received "high risk of bias" rating in 5/7 categories.

<sup>5</sup> Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness

### 6.11.b. Teriparatide vs Oral bisphosphonate

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 67. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR TERIPARATIDE VS ORAL BISPHOSPHONATE IN ADULTS <40 ON HIGH DOSE STEROIDS**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
<b>Hip Fracture</b> <b>18 months</b>	428 (1 RCT) 18 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3,5</sup> due to risk of bias, imprecision	<b>Relative Risk 0.33</b> (0.01 to 8.14)	<b>5 per 1000</b>	<b>3 fewer per 1000</b> (from 5 fewer to 33 more)
<b>Vertebral Fracture</b> <b>36 months</b>	342 (1 RCT) 36 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to imprecision	<b>Relative Risk 0.23</b> (0.07 to 0.78)	<b>77 per 1000</b>	<b>59 fewer per 1000</b> (from 17 fewer to 72 fewer)
<b>Vertebral Fracture</b> <b>18 months</b>	336 (1 RCT) 18 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,5</sup> due to imprecision	<b>Relative Risk 0.1</b> (0.01 to 0.75)	<b>61 per 1000</b>	<b>55 fewer per 1000</b> (from 15 fewer to 60 fewer)

<b>Non-Vertebral Fracture</b> 36 months	428 (1 RCT) 36 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to risk of bias, imprecision	<b>Relative Risk 1.07</b> (0.54 to 2.1)	<b>70 per 1000</b>	<b>5 more per 1000</b> (from 32 fewer to 77 more)
<b>Non-Vertebral Fracture</b> 18 months	428 (1 RCT) 18 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3,5</sup> due to imprecision	<b>Relative Risk 1.5</b> (0.63 to 3.6)	<b>37 per 1000</b>	<b>19 more per 1000</b> (from 14 fewer to 97 more)
<b>Serious Adverse Events</b> 36 months	428 (1 RCT) 36 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to imprecision	<b>Relative Risk 1.06</b> (0.87 to 1.28)	<b>299 per 1000</b>	<b>18 more per 1000</b> (from 39 fewer to 84 more)
<b>Total Adverse Events</b> 36 months	428 (1 RCT) 36 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4,5</sup> due to imprecision	<b>Relative Risk 1.05</b> (0.98 to 1.13)	<b>860 per 1000</b>	<b>43 more per 1000</b> (from 17 fewer to 112 more)

**Bibliography:** [Saag, et al. N Engl J Med. 2007 Nov 15; 357\(20\): 2028-39](#) <sup>[38]</sup>. [Saag, et al. Arthritis Rheum. 2009 Nov; 60\(11\): 3346-55](#) <sup>[39]</sup>

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> 31% discontinuation rate at 18 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> 95% CI is wide

<sup>4</sup> 44% discontinuation rate at 36 months overall. Discontinuations clearly described. Vertebral fracture rates were calculated for patients with baseline and post-baseline radiographs only. Non-vertebral fractures were calculated using the whole sample N; ITT procedure not described.

<sup>5</sup> Per Panel Request, Saag 2007 and Saag 2009 were downgraded from an original grade of “Moderate” to a new grade of “Low” due to small sample size and incredible treatment effects (5/14/16)

### 6.12.b. Denosumab vs Oral bisphosphonate

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.13b Abaloparatide vs oral bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.14b Romosozumab vs oral bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium and vitamin?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.15.b. Teriparatide vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.16.b. Denosumab vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.17.b. Denosumab vs Teriparatide**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with teriparatide, calcium and vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.18b Abaloparatide vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with abaloparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **6.19b Romosozumab vs IV bisphosphonate**

For adults receiving one or more courses of high dose glucocorticoid therapy (mean dose  $\geq 30$  mg daily for  $\geq 30$  days) and cumulative dose  $\geq 5$  gm over one year, what are the benefits and harms of treatment with romosozumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium and vitamin?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## **IX. CHILDREN RECEIVING GLUCOCORTICOIDS FOR GREATER THAN 3 MONTHS TREATMENT QUESTIONS**

#### **7.1.a. Vit D+Ca vs Placebo**

In children ages 4-17 treated with glucocorticoids for greater than 3 months, what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 68. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR CALCIUM AND VITAMIN D VERSUS NO CALCIUM AND VITAMIN D FOR CHILDREN**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Calcium and Vitamin D*	Risk difference with Calcium and Vitamin D (95% CI)**
Hip Fracture				No data	
Vertebral Fracture				No data	
Non-Vertebral Fracture				No data	
Mean % Change Bone Mineral Content (Lumbar Spine) g/cm <sup>2</sup>	41 (1 RCT) 12 weeks	⊕⊕⊕⊕ VERY LOW <sup>1,2,3,4</sup> due to risk of bias, indirectness, imprecision	Mean Difference 20.13 (12.20 to 28.06)	The mean BMC change in the control group was -8.94%	The mean % change bone mineral content for the lumbar spine in the intervention groups was 20.13 higher (12.2 to 28.06 higher)
Mean % Height Gain cm	41 (1 RCT) 12 weeks	⊕⊕⊕⊕ VERY LOW <sup>1,2,3,4</sup> due to risk of bias, indirectness, imprecision	Mean Difference -0.04 (-0.87 to 0.79)	The mean Height Gain in the control group was 1.84%	The mean % height gain in the intervention groups was 0.04 lower (0.87 lower to 0.79 higher)
Mean % Change BMD (Lumbar Spine) g/cm <sup>2</sup>	81 (2 RCTs) 10 weeks	⊕⊕⊕⊕ VERY LOW <sup>1,2,3,5,6</sup> due to risk of bias, inconsistency, indirectness, imprecision	Mean Difference 5.54 (-0.65 to 11.73)	The mean BMD change in the control group ranged from -13% to 0.74%	The mean % change bone mineral density for the lumbar spine in the intervention groups was 5.54 higher (0.65 lower to 11.73 higher)
Serious Adverse Events				No data	

Total Adverse Events			No data	
Hypercalciuria	40 (1 RCT) 8 weeks	⊕⊖⊖⊖ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk</b> <b>0.75</b> (0.32 to 1.77)	<b>400 per 1000</b>  <b>100 fewer per 1000</b> (from 272 fewer to 308 more)

Bibliography: [Bak, et al. Pediatr Nephrol. 2006 Mar; 21\(3\):350-4](#) <sup>[53]</sup>; [Choudhary, et al. Pediatr Nephrol. 2014 Jun;29\(6\):1025-32](#) <sup>[54]</sup>

<sup>1</sup> Participants/personnel not blinded to allocation. No placebo used

<sup>2</sup> Very small sample size

<sup>3</sup> Study duration is under 1 year. We agreed a priori to downgrade any study duration <12 mo for indirectness

<sup>4</sup> Outcome is only assessed by one study.

<sup>5</sup> I<sup>2</sup>=85%; due to significant differences in populations at baseline, direction of change is opposite between the two trials.

<sup>6</sup> 95% CI is wide

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

### 7.2.a Exercise +Ca/Vit D vs no exercise vit D/CA

In children ages 4-17 treated with glucocorticoids for greater than 3 months, what are the benefits and harms of treatment with exercise plus calcium and vitamin D versus treatment with calcium or vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 7.3.a Exercise +CA/Vit D vs exercise

In children ages 4-17 treated with glucocorticoids for greater than 3 months, what are the benefits and harms of treatment with exercise plus calcium and vitamin D versus treatment with exercise alone?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**



#### 7.4.a Exercise vs Ca/VIT D

In children ages 4-17 treated with glucocorticoids for greater than 3 months, what are the benefits and harms of treatment with exercise versus treatment with calcium or vitamin D?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### 7.5.a. Oral bisphosphonate vs Ca/Vit D

In children, ages 4-17 treated with glucocorticoids for greater than 3 months what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

**Summary:** Four RCTs—one identified in the updated literature searches (Rooney et al. 2019) and three pulled forward from the previous review (El-Husseini et al. 2004; Rudge et al. 2005; Bianchi et al. 2013) assessed the use of a bisphosphonates among children who were on long-term glucocorticoids (>1 year). The children in these studies were taking glucocorticoids as part of treatment for the following conditions: cystic fibrosis (Bianchi et al. 2013), renal transplant (El-Husseini, et al. 2004), and chronic rheumatic disease (Rudge, 2005; Rooney, 2019). In all studies, the children had low BMD Z scores for their age (Z score  $\leq -2$  for patients 18 and under or  $\leq -2.5$  for patients over 18). The average age of the children ranged from 8.5 to 15 years.

Three studies compared oral alendronate (5 to 10 mg/day depending on bodyweight) to placebo (El-Husseini et al. 2004; Rudge et al. 2005; Bianchi et al. 2013). Calcium and vitamin D intake varied across studies with children in one study given calcifediol in addition to bisphosphonate or placebo (Bianchi et al. 2013) and children in the other studies given calcium or vitamin D supplements as needed. The fourth study compared alfacalcidol or risedronate plus 500 mg calcium and 400 IU vitamin D to placebo plus calcium and vitamin D (Rooney et al. 2019). This study also compared alfacalcidol to risedronate. The outcomes reported on included fracture, lumbar spine BMD, any adverse event, serious adverse events (not defined in the study), and gastrointestinal adverse events. Not all studies reported on each of these outcomes. Table 2 below presents the findings for each outcome separately.

Very uncertain evidence suggests that there were fewer fractures in the bisphosphonate group than in the control group. However, the difference between groups was minimal and not statistically significant. Similarly, uncertain evidence suggests that bisphosphonates are associated with a slight improvement in lumbar spine BMD compared to placebo at 12-months follow-up. Bisphosphonates, however, appear to be associated with increased risk of serious adverse events. The authors of the study reporting on serious adverse events, however, did not specify the events, and indicated that only 1 of the 21 events was related to the study medication.

- Certainty of evidence across all critical outcomes for GIOP population: Very low

**TABLE 69. SUMMARY OF FINDINGS FOR BISPHOSPHONATE VS. PLACEBO IN CHILDREN ON GLUCOCORTICOID FOR GREATER THAN 3 MONTHS**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS	Control	Relative (95% CI)	Absolute (95% CI)		
Vertebral Fracture												
1	randomized trials	not serious	not serious	serious <sup>a</sup>	very serious <sup>b,c</sup>	none	1/65 (1.5%)	4/63 (6.3%)	Relative Risk <b>0.24</b> (0.03 to 2.11)	<b>48 fewer per 1,000</b> (from 62 fewer to 70 more)	⊕○○○ Very low	
Non-Vertebral Fracture												
4	randomized trials	serious <sup>d</sup>	not serious	serious <sup>a,e</sup>	serious <sup>b</sup>	none	5/230 (2.2%)	8/165 (4.8%)	Relative Risk <b>0.50</b> (0.18 to 1.42)	<b>24 fewer per 1,000</b> (from 40 fewer to 20 more)	⊕○○○ Very low	
Change in Lumbar BMD Z score, 12 months (g/cm <sup>2</sup> )												
2	randomised trials	serious <sup>d</sup>	not serious	serious <sup>e,f</sup>	not serious	none	68	80	-	Mean Difference <b>0.27 higher</b> (0.1 higher to 0.44 higher)	⊕⊕○○ Low	Favors BIS
Total AE												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral BIS	Control	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	not serious	serious <sup>a</sup>	not serious	none	68/134 (50.7%)	72/140 (51.4%)	<b>Relative Risk 1.06</b> (0.91 to 1.22)	<b>31 more per 1,000</b> (from 46 fewer to 113 more)	⊕⊕⊕○ Moderate	
<b>Serious Adverse Event</b>												
1	randomized trials	not serious	not serious	not serious	very serious <sup>b,c</sup>	none	35/139 (25.2%)	18/77 (23.4%)	<b>Odds Ratio 1.10</b> (0.57 to 2.12)	<b>18 more per 1,000</b> (from 86 fewer to 159 more)	⊕⊕○○ Low	

**Bibliography:** Rooney et al. 2019; [El-Husseini, et al. \*Pediatr Transplant\*. 2004 Aug;8\(4\):357-61 \[55\]](#); [Rudge, et al. \*Rheumatology \(Oxford\)\*. 2005 Jun;44\(6\):813-8 \[56\]](#); Bianchi, et al. *Lancet Respir Med*. 2013 Jul;1(5):377-85 [57]

a. Participants in Bianchi 2013 are primarily taking inhalatory GCs (51%), only 30% of sample is taking both inhalatory and systemic GCs

b. 95% confidence intervals wide

c. Single, small study

d. Lack of blinding

e. 1 Participants in El-Husseini are not receiving Vitamin D. Participants in Rudge were not prescribed Calcium or Vitamin D, but supplementation was not prohibited. Participants in Bianchi were taking Vitamin D, but Calcium supplementation was by dietary recommendation, was not a part of the protocol.

f. Bone mineral density is an indirect outcome

CI: confidence interval; BIS: bisphosphonate; MD: mean difference; OR: odds ratio; PLA: placebo; RR: risk ratio

## RISEDRONATE VS ALFACALCIDOL

**Summary:** One RCT identified in the updated literature searches (Rooney et al. 2019) compared the use of risedronate to alfacalcidol among children who were on long-term glucocorticoids (>1 year). The children in these studies were taking glucocorticoids as part of treatment for the chronic rheumatic disease (Rooney, 2019). The children in the study had low BMD Z scores for their age (Z score ≤-2 for patients 18 and under or ≤-2.5 for patients over 18). The average age of the children was 12.1 years. Children in both study groups were also taking 500 mg calcium and

400 IU vitamin D (Rooney et al. 2019). The outcomes reported on included fracture, lumbar spine BMD, any adverse event, serious adverse events (not defined in the study). Table 3 below presents the findings for each outcome separately.

Low quality evidence suggests that slightly more fractures occurred in children taking risedronate compared to alfacalcidol (5/68 (7.4%) vs. 2/71 (2.8%)). However, this difference was not statistically significant. Low quality evidence suggests that children taking risedronate had slightly higher lumbar spine bone mineral density z scores than children taking alfacalcidol. However, risedronate was associated with a higher incidence of serious adverse events. The authors indicate that the event was associated with risedronate in only 1 child.

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 70. SUMMARY OF FINDINGS FOR RISEDRONATE VS. ALFACALCIDOL IN CHILDREN ON GLUCOCORTICOIDS FOR GREATER THAN 3 MONTHS**

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risedronate	Alfacalcidol	Relative (95% CI)	Absolute (95% CI)		
Non-vertebral fracture												
1	randomized trials	not serious	not serious	not serious	very serious <sup>a,b</sup>	none	5/68 (7.4%)	2/71 (2.8%)	<b>Odds Ratio 2.74</b> (0.51 to 14.62)	<b>45 more per 1,000</b> (from 14 fewer to 269 more)	⊕⊕○○ Low	
Lumbar Spine BMD z-score (g/cm <sup>2</sup> )												
1	randomized trials	not serious	not serious	serious <sup>c</sup>	serious <sup>a</sup>	none	69	71	-	Mean Difference <b>0.27 higher</b> (0.11 higher to 0.44 higher)	⊕⊕○○ Low	Favors risedronate

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risedronate	Alfacalcidol	Relative (95% CI)	Absolute (95% CI)		
Any Adverse Event												
1	randomized trials	not serious	not serious	not serious	very serious <sup>a,b</sup>	none	59/69 (85.5%)	59/71 (83.1%)	<b>Odds Ratio 1.20</b> (0.48 to 2.99)	<b>24 more per 1,000</b> (from 129 fewer to 105 more)	⊕⊕○○ Low	
Serious Adverse Event												
1	randomized trials	not serious	not serious	not serious	serious <sup>a</sup>	none	21/59 (35.6%)	14/71 (19.7%)	<b>Odd Ratio 2.25</b> (1.02 to 4.96)	<b>159 more per 1,000</b> (from 3 more to 352 more)	⊕⊕⊕○ Moderate	Favors alfacaidol

**Bibliography:** Rooney et al. 2019;

a. Single study reporting on outcome

b. Wide confidence interval

c. Bone mineral density is an indirect outcome

CI: confidence interval; MD: mean difference; OR: odds ratio

## B. CHILDREN RECEIVING HIGH DOSE GC WITH A SYMPTOMATIC COMPRESSION FRACTURE

**PICO 7.1b:** In children ages 4-17 treated with high dose GCs who have had a symptomatic compression fracture, what are the benefits and harms of treatment with oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

- Certainty of evidence across all critical outcomes for GIOP population: Low

**TABLE 71. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR ORAL BISPHOSPHONATE IN CHILDREN WITH SYMPTOMATIC COMPRESSION FRACTURE**

Outcomes	No of Participants	Certainty of the evidence	Relative effect	Anticipated absolute effects
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	(studies) Follow up	(GRADE)	(95% CI)	Risk with Calcium and Vitamin D*	Risk difference with Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>					
			No data		
<b>Vertebral Fracture</b>	128 (1 RCT) 12 months	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3,4</sup> due to indirectness, imprecision	<b>Relative Risk 0.24</b> (0.03 to 2.11)	<b>63 per 1000</b>	<b>48 fewer per 1000</b> (from 62 fewer to 70 more)
<b>Non-Vertebral Fracture</b>	180 (3 RCTs) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,5</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk 0.28</b> (0.05 to 1.63)	<b>45 per 1000</b>	<b>32 fewer per 1000</b> (from 43 fewer to 28 more)
<b>Mean % Change in volumetric BMD (Lumbar Spine) g/cm<sup>3</sup></b>	131 (2 RCTs) 12 months	⊕⊕⊕⊕ <b>LOW</b> <sup>1,2,3</sup> due to indirectness, imprecision	<b>Mean Difference 14.43</b> (12.85 to 16.02)	The mean vBMD change in the control group ranged from 4.8% to 9.05%	The mean % change in volumetric BMD of the lumbar spine in the intervention groups was <b>14.43 higher</b> (12.85 higher to 16.02 higher)
<b>Change in BMD T score (Lumbar Spine)</b>	30 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,4,5,6</sup> due to risk of bias, indirectness, imprecision	<b>Mean Difference 0.80</b> (0.46 to 1.14)	The mean change in BMD T score in the control group was -0.4	The mean change in BMD T score of the lumbar spine in the intervention groups was <b>0.80 higher</b> (0.46 higher to 1.14 higher)

<b>Change in BMD Z score (Lumbar Spine)</b>	18 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,4,6</sup> due to indirectness, imprecision	<b>Mean Difference 0.24</b> (-0.56 to 1.04)	The mean change in BMD Z score in the control group was 0.37	The mean change in BMD Z score of the lumbar spine in the intervention groups was <b>0.24 higher</b> (0.56 lower to 1.04 higher)
<b>Serious Adverse Events</b>					
			No data		
<b>Total Adverse Events</b>	128 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4</sup> due to indirectness, imprecision	<b>Relative Risk 0.87</b> (0.38 to 2.00)	<b>159 per 1000</b>	<b>21 fewer per 1000</b> (from 98 fewer to 159 more)
<b>Hypocalcaemia</b>	30 (1 RCT) 12 months	⊕⊖⊖⊖ <b>VERY LOW</b> <sup>1,3,4,5,6</sup> due to risk of bias, indirectness, imprecision	<b>Relative Risk 3.00</b> (0.13 to 68.26)	<b>0 per 1000</b>	-
<b>Gastrointestinal Adverse Events</b>	128 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>2,4</sup> due to indirectness, imprecision	<b>Relative Risk 0.69</b> (0.23 to 2.07)	<b>111 per 1000</b>	<b>34 fewer per 1000</b> (from 86 fewer to 119 more)

**Bibliography:** [El-Husseini, et al. \*Pediatr Transplant\*. 2004 Aug;8\(4\):357-61](#) <sup>[55]</sup>; [Rudge, et al. \*Rheumatology \(Oxford\)\*. 2005 Jun;44\(6\):813-8](#) <sup>[56]</sup>; Bianchi, et al. *Lancet Respir Med*. 2013 Jul;1(5):377-85 <sup>[57]</sup>

<sup>1</sup> Participants in El-Husseini are not receiving Vitamin D. Participants in Rudge were not prescribed Calcium or Vitamin D, but supplementation was not prohibited. Participants in Bianchi were taking Vitamin D, but Calcium supplementation was by dietary recommendation, was not a part of the protocol.

<sup>2</sup> Participants in Bianchi 2013 are primarily taking inhalatory GCs (51%), only 30% of sample is taking both inhalatory and systemic GCs

<sup>3</sup> 95% CIs are wide

<sup>4</sup> Outcome is only assessed by one study

<sup>5</sup> El-Husseini is open label. Discontinuation is not reported.

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<sup>6</sup> Very small sample size(s)The **assumed risk\*** is based on the number of events in the control arms across studies.

The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

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**PICO 7.2b: In children ages 4-17 treated with high dose GCs who have had a symptomatic compression fracture, what are the benefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?**

**Summary:** This study was a multi-center RCT that looked at the effects of administering zoledronic acid (ZA) infusions versus only providing vitamin D and calcium on lumbar spine (LS) bone mineral density (BMD) (Zacharin, 2021). Participants included were male patients with glucocorticoid dependent Duchenne Muscular Dystrophy ages between 6-16 years. Sixty-two patients were enrolled, 31 in each arm. The trial involved administering 5 infusions of ZA with calcium and vitamin D supplements in the intervention arm, versus only providing calcium and vitamin D in the control arm. The primary outcome was the LS BMD at 24 months. LS BMD at 12 months and fracture data were secondary outcomes. At 12 and 24 months, LS BMD was higher by 0.10 and 0.13 g/cm<sup>2</sup> in the ZA intervention group ( $P < 0.001$ ), and mean differences in changes of LS BMD from baseline were 19.3% (14.6 to 24.0) at 12 months and 26.0% (17.4 to 34.5) at 24 months in ZA compared with the control arm ( $P < 0.001$ ). There were 4/27 (15%) boys in the ZA intervention arm and 7/29 (24%) boys in the control arm who had new vertebral fractures during the 24 months, with a total of 15 and 16 new fractures in the ZA and control arms, respectively. At 24 months, there was little evidence of a difference in the spinal deformity index between the 2 arms (mean difference 0.22; 95% CI -0.70 to 1.14;  $P = 0.63$ )

Overall, this was a relatively small study with only 62 patients included. There was an attrition rate of >20%. Moreover, participants and clinicians were not blinded during the study (with only the radiologists reading the DXA scans and spine x-rays being blinded to the group allocation).

- **Certainty of evidence across all critical outcomes for GIOP population: Low**

**TABLE 72. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR IV BISPHOSPHONATE IN CHILDREN WITH HIGH DOSE GLUCOCORTICOIDS**

Certainty assessment	No of patients	Effect	Certainty	Importance
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No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zoledronic acid	placebo	Relative (95% CI)	Absolute (95% CI)		
LS BMD_24 mo (g/cm <sup>2</sup> )												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	28	26	-	Mean Difference <b>0.11 higher</b> (0.03 higher to 0.19 higher)	⊕○○○ Very low	Favors ZA
LS BMD_12mo (g/cm <sup>2</sup> )												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	28	26	-	Mean Difference <b>0.09 higher</b> (0.02 higher to 0.16 higher)	⊕○○○ Very low	Favors ZA
New Vertebral Fracture												
1	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c,d</sup>	none	4/27 (14.8%)	7/29 (24.1%)	Relative Risk 0.61 (0.20 to 1.86)	94 fewer per 1,000 (from 193 fewer to 208 fewer)	⊕⊕○○ Low	

**Bibliography: Zacharin et al. 2021**

- a. Participants and clinicians were not blinded. Attrition >20%.
- b. Indirect outcome
- c. Small sample size
- d. Wide confidence intervals

CI: confidence interval; MD: mean difference; RR: risk ratios

## ***X. INITIAL FRACTURE RISK ASSESSMENT VERSUS NO FRACTURE RISK ASSESSMENT QUESTIONS***

### **Adults Over age 40**

#### **8.1.**

In adults  $\geq$  age 40 who are *initiating* oral glucocorticoid therapy expected to last  $\geq$  90 days and who never have had an assessment of fracture risk or been treated with osteoporosis medication, what are the benefits and harms of patient fracture risk assessment (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) (including timing) versus no fracture risk assessment?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **8.2.**

In adults  $\geq$  age 40 *continuing* chronic glucocorticoid therapy and who never have had an assessment of fracture risk or been treated with osteoporosis medication, what are the benefits and harms of patient fracture risk assessment (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) (including timing) versus no fracture risk assessment?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### **Adults under age 40**

#### **8.3**

In adults  $\leq$  age 40 who are *initiating* oral glucocorticoid therapy expected to last  $\geq$  90 days, but who never have had an assessment of fracture risk or been treated with osteoporosis medication, what are the benefits and harms of patient fracture risk assessment (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) (including timing) versus no fracture risk assessment?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **8.4.**

In adults  $\leq$  age 40 **continuing** chronic glucocorticoid therapy and who never have had an assessment of fracture risk or been treated with osteoporosis medication, what are the benefits and harms of patient fracture risk assessment (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) (including timing) versus no fracture risk assessment?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### ***XI. FRACTURE RISK REASSESSMENT QUESTIONS (YES-NO AND EARLY-LATER)***

**Untreated/Low risk – either not recommended or recommended but not treated/ low or high dose GC**

**9.1 In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $<7.5$  mg daily, assessed low fracture risk at initiation of treatment) who did not start (or were not recommended to start) osteoporosis medication (except calcium and vitamin D), what are the benefits and harms of reassessment of patient fracture risk 1-2 years after initial no treatment decision (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) versus no reassessment of patient fracture risk?**

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **9.2.**

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $\geq 7.5$  mg daily, assessed low fracture risk) who did not start (or were not recommended to start) osteoporosis medication (except calcium and vitamin D), what are the benefits and harms of reassessment of patient fracture risk 1-2 years after initial no treatment decision (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) versus no reassessment of patient fracture risk?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**Untreated/Mod risk – either not recommended or recommended but not treated/low dose or high dose GC**

**9.3.**

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $<7.5$  mg daily, assessed medium fracture risk) did not start (or were not recommended to start) osteoporosis medication (except calcium and vitamin D), what are the benefits and harms of reassessment of patient fracture risk 1-2 years after initial no treatment decision (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) versus no reassessment of patient fracture risk?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**9.4.**

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $\geq 7.5$  mg daily, assessed medium fracture risk) did not start (or were not recommended to start) osteoporosis medication (except calcium and vitamin D), what are the benefits and harms of reassessment of patient fracture risk 1-2 years after initial no treatment decision (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) versus no reassessment of patient fracture risk?

**Adults currently taking GIOP Treatment, looking at reassessment to decide whether to continue current treatment, stop treatment or change treatment**

***Reassessment/no reassessment, high and low dose,***

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**9.5.**

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $<7.5$  mg daily, medium or high fracture risk assessment), continuing osteoporosis medication for  $\geq 1$  year but  $<3-5$  years), what are the benefits and harms of any reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) at least 1 year after starting osteoporosis medication versus no reassessment of patient fracture risk?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**9.6.**

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $\geq 7.5$  mg daily, medium or high fracture risk assessment), continuing osteoporosis medication for  $\geq 1$  year but  $<3-5$  years, what are the benefits and harms of any reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) at least 1 year after starting osteoporosis medication versus no reassessment of patient fracture risk?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**FRACTURE RISK REASSESSMENT QUESTIONS AFTER COMPLETING A FULL COURSE OF OP MEDICATION - (YES/NO, EARLY/LATE, HIGH AND LOW DOSE GC)**

**YES/NO**

#### **9.7.**

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $< 7.5$  mg daily, assessed as medium or high fracture risk), and [who have completed a full course of osteoporosis medication](#), what are the benefits and harms of reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) (e.g., 2 years after the osteoporosis medication was stopped) versus no reassessment of patient fracture risk?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **9.8**

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $\geq 7.5$  mg daily, assessed as medium or high fracture risk), and [who have completed a full course of osteoporosis medication](#), what are the benefits and harms of reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) (e.g., 2 years after the osteoporosis medication was stopped) versus no reassessment of patient fracture risk?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**Timing of reassessment: EARLY/LATE**

### 9.9

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $<7.5$  mg daily, assessed as medium or high fracture risk), and [who have completed a full course of bisphosphonate osteoporosis medication](#), what are the benefits and harms of early reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays symptomatic fracture history) (e.g., 1-2 years after the osteoporosis medication was stopped) versus later reassessment of patient fracture risk (e.g.,  $\geq 3$  years after the osteoporosis medication was stopped)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**9.10.** In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $<7.5$  mg daily, assessed as medium or high fracture risk), and [who have completed a full course of non-bisphosphonate osteoporosis medication](#) (e.g., denosumab, PTH analog, romosozumab), what are the benefits and harms of early reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays symptomatic fracture history) (e.g., 6 months after the osteoporosis medication was stopped) versus later reassessment of patient fracture risk (e.g.,  $\geq 1$  years after the osteoporosis medication was stopped)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 9.11

In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $\geq 7.5$  mg daily, assessed as medium or high fracture risk), and [who have completed a full course of bisphosphonate osteoporosis medication](#), what are the benefits and harms of early reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays symptomatic fracture history) (e.g., 1-2 years after the osteoporosis medication was stopped) versus later reassessment of patient fracture risk (e.g.,  $\geq 3$  years after the osteoporosis medication was stopped)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**9.12** In adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose  $\geq 7.5$  mg daily, assessed as medium or high fracture risk), and [who have completed a full course of non-bisphosphonate osteoporosis medication](#) (e.g., denosumab, PTH analog, or romosozumab) what are the benefits and harms of early reassessment of patient fracture risk (e.g., FRAX, BMD, VFA, spine x-rays symptomatic fracture history) (e.g., 3-6 months after the osteoporosis medication was stopped) versus later reassessment of patient fracture risk (e.g.,  $\geq 1$  years after the osteoporosis medication was stopped)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## ***XII. BISPHOSPHONATE TREATMENT FAILURE TREATMENT QUESTIONS***

### **10.1. CONTINUE VS SWITCH IV BIS**

For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to an IV bisphosphonate (though continuing calcium and vitamin D) compared to continuing the current oral bisphosphonate?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Moderate (based on adverse event outcomes only)**

**TABLE 73. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION SWITCHING TO IV BISPHOSPHONATE**

		Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	Risk difference with Switching to IV Bisphosphonate (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events	225 (1 RCT) 12 months	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	Relative Risk 1.08 (0.5 to 2.35)	98 per 1000	8 more per 1000 (from 49 fewer to 133 more)
Total Adverse Events	225 (1 RCT) 12 months	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	Relative Risk 1.08 (0.96 to 1.21)	804 per 1000	64 more per 1000 (from 32 fewer to 169 more)

**Bibliography:** [McClung, et al. Bone. 2007 Jul; 41\(1\):122-8. \[58\]](#)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

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CI: Confidence interval; RR: Risk ratio;

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<sup>1</sup> Outcome is only assessed by one study

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### 10.2. CONTINUE vs SWITCH to Teriparatide

For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to teriparatide (though continuing calcium and vitamin D) compared to continuing the current an oral bisphosphonate?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### 10.3. CONTINUE vs SWITCH to Denosumab of an oral bisphosphonate

For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate what are the benefits and harms of switching to denosumab (though continuing calcium and vitamin D) compared to continuing the current an oral bisphosphonate?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 74. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR SWITCHING TO DENOSUMAB IN ADULTS  $\geq$ 40 WITH GIOP**

**Bibliography:** [Mok, et al. Bone. 2015 Jun;75:222-8](#) <sup>[59]</sup>.

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	Risk difference with Switching to Denosumab (95% CI)**
<b>Hip Fracture</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	Not estimable	No incidence of Hip Fracture in either group over 12 months	
<b>Vertebral Fracture</b>	42 (1 RCT)	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup>	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	



	12 months	due to risk of bias, imprecision		
<b>Non-Vertebral Fracture</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months
<b>Serious Adverse Events</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	Not estimable	No incidence of Serious Adverse Events in either group over 12 months
<b>Total Adverse Events</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>3.6</b> (1.64 to 7.89)	<b>238 per 1000</b>  <b>619 more per 1000</b> (from 152 more to 1000 more)
<b>Infections</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk</b> <b>7.0</b> (0.94 to 52.04)	<b>48 per 1000</b>  <b>286 more per 1000</b> (from 3 fewer to 1000 more)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Open label trial

<sup>2</sup> Very small sample size

<sup>3</sup> Outcome only assessed by one study

<sup>4</sup> Due to zero events, effect was inestimable

**10.4. CONTINUE vs SWITCH to Abaloparatide** For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to Abaloparatide (though continuing calcium and vitamin D) compared to continuing the current an oral bisphosphonate?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**10.5. CONTINUE vs SWITCH to Romosozumab** For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density after 2 years of an oral bisphosphonate or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to Romosozumab (though continuing calcium and vitamin D) compared to continuing the current an oral bisphosphonate?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **10.6 IV bisphosphonate vs Teriparatide**

For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to IV bisphosphonate (though continuing calcium and vitamin D) compared switch to teriparatide?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **10.7 IV bisphosphonate vs Denosumab**

For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to IV bisphosphonate (though continuing calcium and vitamin D) compared to switching to denosumab?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

#### **10.8 Teriparatide vs Denosumab**

For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to teriparatide (though continuing calcium and vitamin D) compared to switching to denosumab?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**10.9 Teriparatide plus Denosumab** For adults  $\geq$  age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 12 months of an oral bisphosphonate, what are the benefits and harms of switching to teriparatide plus denosumab (though continuing calcium and vitamin D) compared to switching to either teriparatide or denosumab?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### ***XIII. DISCONTINUING GLUCOCORTICOID THERAPY QUESTIONS***

#### **11.1.**

For adults  $\geq$  40 taking osteoporosis medication in addition to calcium and vitamin D , and discontinuing oral glucocorticoid therapy and assessed to be of low fracture risk, what are the benefits and harms of stopping the current osteoporosis medication (though continuing calcium and vitamin D) compared to continuing current osteoporosis medication?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

### ***XIV. TREATMENT IF HIGH RISK AFTER COMPLETING FULL COURSE ORAL BISPHOSPHONATE QUESTIONS***

#### **HIGH RISK**

#### **12.1.**

For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral bisphosphonate (e.g., 3-5 years of treatment), and are considered high fracture risk (high risk FRAX, BMD T-score < -2.5, or history of fragility fracture) while on therapy, what are the benefits and harms of continuing oral bisphosphonate treatment versus stopping osteoporosis medication (though continuing calcium and vitamin D)?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 75. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION DISCONTINUING ORAL BISPHOSPHONATE**

Outcomes	No of Participants	Certainty of the	Relative	Anticipated absolute effects
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	(studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Continuing Oral Bisphosphonate*	Risk difference with Discontinuing Oral Bisphosphonate (95% CI)**
<b>Hip Fracture</b>	1099 (1 RCT) 5 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk 0.98</b> (0.5 to 1.96)	<b>30 per 1000</b>	<b>1 fewer per 1000</b> (from 15 fewer to 29 more)
<b>Vertebral Fracture</b>	1449 (2 RCTs) 3.5 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk 1.15</b> (0.82 to 1.6)	<b>84 per 1000</b>	<b>13 more per 1000</b> (from 15 fewer to 50 more)
<b>Non-Vertebral Fracture</b>	1515 (3 RCTs) 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>2</sup> due to risk of bias	<b>Relative Risk 1.03</b> (0.81 to 1.3)	<b>153 per 1000</b>	<b>5 more per 1000</b> (from 29 fewer to 46 more)
<b>Serious Adverse Events</b>	350 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk 1.39</b> (0.75 to 2.58)	<b>94 per 1000</b>	<b>37 more per 1000</b> (from 23 fewer to 148 more)
<b>Total Adverse Events</b>	350 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk 1.03</b> (0.95 to 1.11)	<b>881 per 1000</b>	<b>26 more per 1000</b> (from 44 fewer to 97 more)

**Bibliography:** [Tonino, et al. J Clin Endocrinol Metab. 2000 Sep;85\(9\):3109-15 \[62\]](#); [Black, et al. JAMA. 2006 Dec 27;296\(24\):2927-38 \[63\]](#); [Michalská, et al. J Clin Endocrinol Metab. 2006 Mar;91\(3\):870-7 \[64\]](#)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> One trial includes an open label arm

**12.2.** For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral bisphosphonate (e.g., 3-5 years of treatment), and are considered high fracture risk (high risk FRAX, BMD T-score < -2.5, or history of fragility fracture while on therapy), what are

the benefits and harms of continuing oral bisphosphonate treatment versus switching to an IV bisphosphonate (though continuing calcium and vitamin D)?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 76. EVIDENCE AVAILABLE FOR GENERAL OSTEOPOROSIS POPULATION SWITCHING TO IV BISPHOSPHONATE**

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	Risk difference with Switching to IV Bisphosphonate (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events	225 (1 RCT) 12 months	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	Relative Risk 1.08 (0.5 to 2.35)	98 per 1000	8 more per 1000 (from 49 fewer to 133 more)
Total Adverse Events	225 (1 RCT) 12 months	⊕⊕⊕⊖ MODERATE <sup>1</sup> due to imprecision	Relative Risk 1.08 (0.96 to 1.21)	804 per 1000	64 more per 1000 (from 32 fewer to 169 more)

**Bibliography:** [McClung, et al. Bone. 2007 Jul; 41\(1\):122-8. \[58\]](#)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Outcome is only assessed by one study

### 12.3.

For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral bisphosphonate (e.g., 3-5 years of treatment), and are considered high fracture risk (high risk FRAX, BMD T-score < -2.5, or history of fragility fracture while on therapy), what are the benefits and harms of continuing oral bisphosphonate treatment versus switching to an osteoporosis medication in another class (though continuing calcium and vitamin D)?

- Certainty of evidence across all critical outcomes for GIOP population: Very low

\*All participants included in studies which comprise GIOP evidence provided below switched from Oral Bisphosphonate to Denosumab

TABLE 75. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR SWITCHING TO ANOTHER CLASS IN GIOP AND GENERAL POPULATION

Bibliography: [Kendler, et al. J Bone Miner Res. 2010 Jan;25\(1\):72-81](#); [Roux, et al. Bone. 2014 Jan;58:48-54](#) <sup>[65]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	Risk difference with Switching to Another Class** (95% CI)
Hip Fracture				No data	
Vertebral Fracture	502 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	
Non-Vertebral Fracture	502 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2,4</sup> due to risk of bias, imprecision	Relative Risk 1.97 (0.6 to 6.45)	16 per 1000	16 more per 1000 (from 6 fewer to 88 more)
Serious Adverse Events	1360 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to risk of bias	Relative Risk 0.94 (0.64 to 1.37)	75 per 1000	5 fewer per 1000 (from 27 fewer to 28 more)
Total Adverse Events	1360 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to risk of bias	Relative Risk 0.95 (0.89 to 1.03)	721 per 1000	36 fewer per 1000 (from 79 fewer to 22 more)
Infections	502 (1 RCT) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	Relative Risk 1.17 (0.95 to 1.45)	373 per 1000	63 more per 1000 (from 19 fewer to 168 more)

<b>Malignancies</b>	1360 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to risk of bias	<b>Relative Risk 0.88</b> (0.44 to 1.74)	<b>25 per 1000</b>	<b>3 fewer per 1000</b> (from 14 fewer to 19 more)
<b>Death</b>	1360 (2 RCTs) 12 months	⊕⊕⊖⊖ <b>LOW</b> <sup>1,4</sup> due to risk of bias, imprecision	<b>Relative Risk 0.99</b> (0.1 to 9.52)	<b>1 per 1000</b>	<b>0 fewer per 1000</b> (from 1 fewer to 13 more)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Open label trial(s)

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> Due to zero events, effect of one or more study(ies) is inestimable

<sup>4</sup> 95%CI is wide

## MODERATE RISK

### 12.4.

For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral bisphosphonate (e.g., 3-5 years of treatment), and are considered to have moderate fracture risk (moderate risk FRAX, BMD T-score ≥ -2.5, and no history of fragility fracture), what are the benefits and harms of continuing oral bisphosphonate treatment versus stopping osteoporosis medication (though continuing calcium and vitamin D)?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 77. EVIDENCE AVAILABLE FOR DISCONTINUING ORAL BISPHOSPHONATE IN GENERAL OSTEOPOROSIS POPULATION:**

**Bibliography:** [Tonino, et al. J Clin Endocrinol Metab. 2000 Sep;85\(9\):3109-15 \[62\]](#); [Black, et al. JAMA. 2006 Dec 27;296\(24\):2927-38 \[63\]](#); [Michalská, et al. J Clin Endocrinol Metab. 2006 Mar;91\(3\):870-7 \[64\]](#)

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate	Risk difference with Discontinuing Oral Bisphosphonate (95% CI)

<b>Hip Fracture</b>	1099 (1 RCT) 5 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk</b> 0.98 (0.5 to 1.96)	<b>30 per 1000</b>	<b>1 fewer per 1000</b> (from 15 fewer to 29 more)
<b>Vertebral Fracture</b>	1449 (2 RCTs) 3.5 years	⊕⊕⊕⊕ <b>HIGH</b>	<b>Relative Risk</b> 1.15 (0.82 to 1.6)	<b>84 per 1000</b>	<b>13 more per 1000</b> (from 15 fewer to 50 more)
<b>Non-Vertebral Fracture</b>	1515 (3 RCTs) 3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>2</sup> due to risk of bias	<b>Relative Risk</b> 1.03 (0.81 to 1.3)	<b>153 per 1000</b>	<b>5 more per 1000</b> (from 29 fewer to 46 more)
<b>Serious Adverse Events</b>	350 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk</b> 1.39 (0.75 to 2.58)	<b>94 per 1000</b>	<b>37 more per 1000</b> (from 23 fewer to 148 more)
<b>Total Adverse Events</b>	350 (1 RCT) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	<b>Relative Risk</b> 1.03 (0.95 to 1.11)	<b>881 per 1000</b>	<b>26 more per 1000</b> (from 44 fewer to 97 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Outcome only assessed by one study

<sup>2</sup> One trial includes an open label arm

## 12.5.

For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral bisphosphonate (e.g., 3-5 years of treatment), and are considered moderate fracture risk (moderate risk FRAX, BMD T-score < -2.5, or history of fragility fracture), what are the benefits and harms of continuing oral bisphosphonate treatment versus switching to an IV bisphosphonate (though continuing calcium and vitamin D)?

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**



TABLE 78. EVIDENCE AVAILABLE FOR SWITCHING TO IV BISPHOSPHONATE IN GENERAL POPULATION

Bibliography: [McClung, et al. Bone. 2007 Jul; 41\(1\):122-8. \[58\]](#)

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	Risk difference with Switching to IV Bisphosphonate (95% CI)**
Hip Fracture				No data	
Vertebral Fracture				No data	
Non-Vertebral Fracture				No data	
Serious Adverse Events	225 (1 RCT) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	RR 1.08 (0.5 to 2.35)	98 per 1000	8 more per 1000 (from 49 fewer to 133 more)
Total Adverse Events	225 (1 RCT) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to imprecision	RR 1.08 (0.96 to 1.21)	804 per 1000	64 more per 1000 (from 32 fewer to 169 more)

The **assumed risk**\* is based on the number of events in the control arms across studies. The **corresponding risk**\*\* (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

<sup>1</sup> Outcome is only assessed by one study

## 12.6.

For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral bisphosphonate (e.g., 3-5 years of treatment), and are considered to have moderate fracture risk (moderate risk FRAX, BMD T-score  $\geq -2.5$ , and no history of fragility fracture), what are the benefits and harms of continuing oral bisphosphonate treatment versus switching to an osteoporosis medication in a different drug class (though continuing calcium and vitamin D)?

**\*All participants included in studies which comprise GIOP and General Osteoporosis evidence provided below switched from Oral Bisphosphonate to Denosumab.**

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 79. SUMMARY OF FINDINGS FOR GIOP POPULATION FOR SWITCHING TO ORAL BISPHOSPHONATE TO DENOSUMAB**

**Bibliography:** Mok, et al. Bone. 2015 Jun;75:222-8. <sup>[59]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	Risk difference with Switching to Another Class (95% CI)**
<b>Hip Fracture</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	Not estimable	No incidence of Hip Fracture in either group over 12 months	
<b>Vertebral Fracture</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	
<b>Non-Vertebral Fracture</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months	
<b>Serious Adverse Events</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3,4</sup> due to risk of bias, imprecision	Not estimable	No incidence of Serious Adverse Events in either group over 12 months	
<b>Total Adverse Events</b>	42 (1 RCT) 12 months	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	<b>Relative Risk 3.6</b> (1.64 to 7.89)	<b>238 per 1000</b>	<b>619 more per 1000</b> (from 152 more to 1000 more)
<b>Infections</b>	42 (1 RCT)	⊕⊕⊕⊕ <b>VERY LOW</b> <sup>1,2,3</sup>	<b>Relative Risk 7.0</b> (0.94 to 52.04)	<b>48 per 1000</b>	<b>286 more per 1000</b> (from 3 fewer to 1000 more)

12 months	due to risk of bias, imprecision	
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The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Open label trial

<sup>2</sup> Very small sample size

<sup>3</sup> Outcome only assessed by one study

<sup>4</sup> Due to zero events, effect was inestimable

**TABLE 80. EVIDENCE AVAILABLE FOR SWITCHING TO ORAL BISPHOSPHONATE TO DENOSUMAB GENERAL OSTEOPOROSIS POPULATION**

**Bibliography:** [Kendler, et al. J Bone Miner Res. 2010 Jan;25\(1\):72-81](#); [Roux, et al. Bone. 2014 Jan;58:48-54](#) <sup>[65]</sup>

Outcomes	No of Participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	Risk difference with Switching to Another Class** (95% CI)
Hip Fracture			No data		
Vertebral Fracture	502 (1 RCT) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,3</sup> due to risk of bias, imprecision	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	
Non-Vertebral Fracture	502 (1 RCT) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2,4</sup> due to risk of bias, imprecision	<b>Relative Risk 1.97</b> (0.6 to 6.45)	<b>16 per 1000</b>	<b>16 more per 1000</b> (from 6 fewer to 88 more)
Serious Adverse Events	1360 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to risk of bias	<b>Relative Risk 0.94</b> (0.64 to 1.37)	<b>75 per 1000</b>	<b>5 fewer per 1000</b> (from 27 fewer to 28 more)
Total Adverse Events	1360 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>1</sup> due to risk of bias	<b>Relative Risk 0.95</b> (0.89 to 1.03)	<b>721 per 1000</b>	<b>36 fewer per 1000</b> (from 79 fewer to 22 more)

<b>Infections</b>	502 (1 RCT) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,2</sup> due to risk of bias, imprecision	<b>Relative Risk 1.17</b> (0.95 to 1.45)	<b>373 per 1000</b>	<b>63 more per 1000</b> (from 19 fewer to 168 more)
<b>Malignancies</b>	1360 (2 RCTs) 12 months	⊕⊕⊕⊕ <b>MODERATE</b> <sup>1</sup> due to risk of bias	<b>Relative Risk 0.88</b> (0.44 to 1.74)	<b>25 per 1000</b>	<b>3 fewer per 1000</b> (from 14 fewer to 19 more)
<b>Death</b>	1360 (2 RCTs) 12 months	⊕⊕⊕⊖ <b>LOW</b> <sup>1,4</sup> due to risk of bias, imprecision	<b>Relative Risk 0.99</b> (0.1 to 9.52)	<b>1 per 1000</b>	<b>0 fewer per 1000</b> (from 1 fewer to 13 more)

The **assumed risk\*** is based on the number of events in the control arms across studies. The **corresponding risk\*\*** (and its 95% confidence interval) is based on the assumed risk and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

<sup>1</sup> Open label trial(s)

<sup>2</sup> Outcome only assessed by one study

<sup>3</sup> Due to zero events, effect of one or more study(ies) is inestimable

<sup>4</sup> 95%CI is wide

## ***XV. SEQUENTIAL THERAPY TREATMENT QUESTIONS***

### **LOW RISK**

**13.1.** For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral denosumab and are considered to have LOW fracture risk (moderate risk FRAX, BMD T-score  $\geq -2.5$ , and no history of fragility fracture), what are the benefits and harms of stopping denosumab treatment without adding a bisphosphonate versus stopping denosumab?

**Summary:** The literature searches identified a series of studies reporting on the efficacy and safety of treating post-menopausal women with low bone mineral density (BMD, T score of  $-2.5$  to  $-3.5$  at the total hip or femoral neck) with romosozumab (ROMO). The first set of four studies reported on changes in BMD among a group of 416 women who began treatment with ROMO for 12 months and after a course of 48 months transitioned to Zolendronate or no treatment for 24 months. The first of this set of studies was a dose finding study that compared the outcomes of women receiving various doses of ROMO to placebo or to open-label alendronate or teriparatide for 12 months (McClung et al.

2014). The second was an extension of the dose finding study in which women who received 12-months of ROMO (at any dose) were re-randomized to transition from ROMO to denosumab (DENO) or to placebo for 24 months (McClung et al. 2018). The findings of this study are the primary focus in this review as the methodology (randomization) meets inclusion criteria and the treatment sequence is related to the PICO questions covered in this review. In the third study, all patients were transitioned from DENO or placebo to 12 months of ROMO (data from this trial was not considered as all patients received ROMO)(Kendler et al. 2019). In the final study, patients remaining in the ROMO only study were non-randomly selected (based on investigator criteria) to discontinue ROMO and either receive up to two years of Zoledronate or no further treatment (McClung et al. 2020).

The second set of two studies, the FRAME studies, assessed the efficacy and safety of transitioning from ROMO to DENO on incidence of fractures at 24 and 36 months. The first of this set of studies, the original FRAME study (Cosman et al. 2016), randomized 7180 women to receive subcutaneous injections of romosozumab (ROMO, at a dose of 210 mg) or placebo monthly for 12 months. Thereafter, patients in each group received open-label denosumab for 12 months, at a dose of 60 mg, administered subcutaneously every 6 months (placebo to denosumab, n=3591; ROMO to denosumab, n=3589). The co-primary outcomes were the cumulative incidence of new vertebral fractures at 12 months and 24 months. Secondary outcomes included clinical (a composite of nonvertebral and symptomatic vertebral) and nonvertebral fractures. Women who completed the 24-month study period were then enrolled in the second trial, the FRAME extension study (Lewiecki et al. 2019), in which they received an additional 12 months of denosumab. The FRAME extension study reported on fracture risk through 36 months among 3042 women transitioning from placebo to denosumab and 3003 transitioning from ROMO to denosumab.

See Table 81 below for further details about these studies. All patients continued to receive calcium >1 g and vitamin D >800 IU throughout the duration of these studies. The risk of bias for the trials that assessed the transition from one treatment to another were rated high for lack of blinding of patients during open-label transitions and unclear for blinding of outcome assessors. Further, evidence from these trials is considered indirect primarily because the patient population in the trials does not include patients with GIOP. Patients on systemic glucocorticoid (≥5 mg of prednisone equivalent per day for >10 days) within the previous 3 months were excluded from these studies. It is also indirect because it does not follow the exact treatment sequence described in the PICO question.

**TABLE 81. DESCRIPTION OF STUDIES ON TREATING POST-MENOPAUSAL WOMEN WITH ROMOSOZUMAB**

Reference	Trial	Intervention (n)	Follow-up
<b>ROMO to Zoledronate</b>			
McClung et al. 2014	Romosozumab double blind period (randomized)	<ul style="list-style-type: none"> <li>Romosozumab (70 mg, 140 mg, or 210 mg QM, or 140 mg or 210 mg every 3 months [Q3M], subcutaneous [SC], n=261)</li> <li>Placebo (n=52)</li> </ul>	12 months

Reference	Trial	Intervention (n)	Follow-up
		<ul style="list-style-type: none"> <li>Alendronate (70 mg, n=51)</li> <li>Teriparatide (20 µg SC, n=55)</li> </ul>	
McClung et al. 2018*  Primary study for ACR review	Denosumab extension period (re-randomized)	Romosozumab to denosumab (60 mg, Q6M, n=90) Romosozumab to placebo (n=93)  (Women who originally received teriparatide received no further treatment; < 25 women went from alendronate to denosumab)	24 months
Kendler et al. 2019	Romosozumab second course (not randomized)	<ul style="list-style-type: none"> <li>All patients to Romosozumab (n=167)</li> </ul>	12 months
McClung et al 2020	Zoledronate follow-up period (not randomized)	<ul style="list-style-type: none"> <li>Romosozumab to no further treatment (n=51)</li> <li>Romosozumab to Zoledronate (5 mg IV, single dose, n=90)</li> </ul>	48 to 72 months
<b>FRAME Studies</b>			
Cosman et al. 2016  Primary study for ACR review	FRAME	<ul style="list-style-type: none"> <li>Romosozumab (210 mg) to denosumab (60 mg) (n=3589)</li> <li>Placebo to denosumab (n=3591)</li> </ul>	24 months
Lewiecki et al. 2019  Primary study for ACR review	FRAME Extension	<ul style="list-style-type: none"> <li>Romosozumab (210 mg) to denosumab (60 mg) (n=3003)</li> <li>Placebo to denosumab (n=3042)</li> </ul>	36 months

At 36 months, very low certainty of evidence suggests that patients who transitioned from ROMO to DENO continued to accrue improvement in BMD compared to patients who transitioned from ROMO to placebo (no treatment)(McClung et al. 2018). Patients in the ROMO to placebo group experienced decreases in BMD similar to pre-treatment levels. There were no differences in any adverse events between ROMO to placebo (75.6%) compared to ROMO to DENO (79.2%). Similarly, there was no statistically significant difference in fragility fractures between ROMO to placebo (3.9%) compared to ROMO to DENO (3.2%). One death occurred in each treatment group.

At 24 months, low certainty evidence found that rates of new vertebral fractures were significantly lower in the ROMO group than in the placebo group after each group made the transition to DENO. ROMO to DENO was associated with 75% lower risk in new fractures compared to ROMO to placebo (0.6% [21 of 3325 patients] vs. 2.5% [84 of 3327], respectively)(Cosman et al. 2016). Similar findings were observed for non-vertebral fracture and clinical fracture at 24 months. Also at 24 months, adverse events, including instances of hyperostosis, cardiovascular events, osteoarthritis, and cancer were balanced between the groups. One atypical femoral fracture and two cases of osteonecrosis of the jaw were observed in the ROMO group. Through 36 months, low certainty evidence found that fracture risk was reduced in patients receiving ROMO versus placebo for 12 months followed by 24 months of DENO: new vertebral fracture (relative risk reduction [RR], 66%; incidence, 1.0% versus 2.8%;  $p < 0.001$ )( Lewiecki et al.) Similar findings were found for clinical fracture and nonvertebral fracture. Adverse events such as cardiovascular events, osteoarthritis, and malignancy were balanced between the groups. Very few adverse events were noted in the ROMO group.

Finally, in McClung et al. 2020, women who had begun treatment with ROMO for 12 months, transitioned to DENO for 12 month, and then received another 12 months of ROMO were selected by investigators to receive no further treatment (n=51) or transition from ROMO to a single dose of zoledronate (n=90). Subjects were followed for an additional 24 months (from month 48 to 72). The findings of the final phase suggest that in women receiving zoledronate after ROMO/DENO/ROMO, lumbar spine, total hip, and femoral neck BMD was generally maintained from months 0 to 72. However, in women who received no further treatment, BMD amounts decreased. For instance, in the no treatment group, lumbar spine BMD decreased by 10.8% from months 48 to 72, but remained 4.2% above baseline levels. See Table 83 for further details about the findings of the transition to zoledronate or no treatment.

- **Certainty of evidence across all critical outcomes for the GIOP population: Very Low**

**TABLE 82. EVIDENCE AVAILABLE FOR ROMOSUZUMAB TO DENOSUMAB IN GENERAL POPULATION**

Certainty assessment							No of patients		Effect	Certainty		Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROMO (any dose) to DENO (60 mg)	ROMO to PLA	Relative (95% CI)	Absolute (95% CI)		
Lumbar Spine-BMD (g/cm <sup>2</sup> ) 36 Months (ROMO->DENO vs ROMO->PLA)(McClung et al., 2018)												

Certainty assessment							No of patients		Effect	Certainty		Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROMO (any dose) to DENO (60 mg)	ROMO to PLA	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	very serious <sup>b,c</sup>	not serious	none	86	87	-	Mean Difference <b>10.5 higher</b> (9.48 higher to 11.52 higher)	⊕○○○ Very low	Favors ROMO to DENO
<b>Total HIP BMD (g/cm<sup>2</sup>) at 36 mos (ROMO-&gt;DENO vs ROMO-&gt;PLA) (McClung et al., 2018)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	very serious <sup>b,c</sup>	not serious	none	85	84	-	Mean Difference <b>5.4 higher</b> (4.56 higher to 6.24 higher)	⊕○○○ Very low	Favors ROMO to DENO
<b>Femoral Neck BMD (g/cm<sup>2</sup>) at 36 mos (ROMO-&gt;DENO vs ROMO-&gt;PLA)(McClung et al., 2018)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	very serious <sup>b,c</sup>	not serious	none	85	84	-	Mean Difference <b>5 higher</b> (3.94 higher to 6.06 higher)	⊕○○○ Very low	Favors ROMO to DENO
<b>Incidence of new vertebral fracture at 24 months (Cosman et al., 2016)</b>												



Certainty assessment							No of patients		Effect	Certainty		Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROMO (any dose) to DENO (60 mg)	ROMO to PLA	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	21/3325 (0.6%)	84/3327 (2.5%)	<b>Relative Risk 0.25</b> (0.16 to 0.40)	<b>19 fewer per 1,000</b> (from 21 fewer to 15 fewer)	⊕⊕○○ Low	Favors ROMO to DENO
<b>Incidence of non-vertebral fracture at 24 months (Cosman et al., 2016)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	96/3589 (2.7%)	129/3591 (3.6%)	<b>RR 0.74</b> (0.57 to 0.97)	<b>9 fewer per 1,000</b> (from 15 fewer to 1 fewer)	⊕⊕○○ Low	Favors ROMO to DENO
<b>Incidence of clinical fracture at 24 months (Cosman et al., 2016)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	99/3589 (2.8%)	147/3591 (4.1%)	<b>Relative Risk 0.67</b> (0.52 to 0.87)	<b>14 fewer per 1,000</b> (from 20 fewer to 5 fewer)	⊕⊕○○ Low	Favors ROMO to DENO
<b>Incidence of new vertebral fracture at 36 months (Lewiecki et al., 2019)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	32/3327 (1.0%)	94/3327 (2.8%)	<b>Relative Risk 0.34</b> (0.23 to 0.51)	<b>19 fewer per 1,000</b> (from 22 fewer to 14 fewer)	⊕⊕○○ Low	Favors ROMO to DENO
<b>Incidence of clinical fracture at 36 months (Lewiecki et al., 2019)</b>												

Certainty assessment							No of patients		Effect	Certainty		Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROMO (any dose) to DENO (60 mg)	ROMO to PLA	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	143/3589 (4.0%)	196/3591 (5.5%)	Relative Risk 0.73 (0.59 to 0.90)	15 fewer per 1,000 (from 22 fewer to 5 fewer)	⊕⊕○○ Low	Favors ROMO to DENO
<b>Incidence of non-vertebral fracture at 36 months (Lewiecki et al., 2019)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	139/3589 (3.9%)	176/3591 (4.9%)	Relative Risk 0.79 (0.64 to 0.98)	10 fewer per 1,000 (from 18 fewer to 1 fewer)	⊕⊕○○ Low	Favors ROMO to DENO

CI: confidence interval; MD: mean difference

a. unclear blinding of outcomes assessors

b. indirect population (not GIOP)

c. indirect outcome

**TABLE 83. EVIDENCE AVAILABLE FOR TRANSITION FROM ROMOSUZUMAB TO ZOLEDRONATE OR NO TREATMENT IN GENERAL POPULATION**

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
McClung et al 2020	Long-term extension of patients who took ROMO for 12 months, followed by DENO for 24 months, followed by ROMO to 12 months were randomized to one dose of Zoledronate or no further treatment	48 to 72 months	Post-menopausal women with low bone mineral density with an mean age of 70.3	<ul style="list-style-type: none"> <li>Romozosumab to no further treatment (n=51)</li> <li>Romozosumab to Zoledronate (ZOL, 5 mg IV, single dose, n=90)</li> </ul>	<p><b><u>Patients no longer receiving treatment</u></b></p> <ul style="list-style-type: none"> <li><b>Lumbar spine BMD:</b> -10.8% (-12.1 to -9.5), represents a decrease of 17.3% during study months (48 to 72); however, it is an increase of 4.3% from baseline amounts</li> <li><b>Total hip BMD:</b> -6.4% (-7.4 to</li> </ul>

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					<p>-5.3)</p> <ul style="list-style-type: none"> <li><b>Femoral neck BMD:</b> -5.9% (-7.2 to -4.7)</li> </ul> <p>Patients transitioned from ROMO to ZOL</p> <ul style="list-style-type: none"> <li><b>Lumbar spine BMD:</b> -0.8 (-1.6 to 0.0), represents a change of 12.8% during study months (baseline to 72 months)</li> <li><b>Total hip BMD:</b> 0.1% (-0.5 to 0.7)</li> <li><b>Femoral neck BMD:</b> 0.5% (-0.4 to 1.3)</li> </ul> <p>Adverse events similar, with no new safety signals observed.</p>

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**13.2.** For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral teriparatide (1-2years and are considered to have LOW fracture risk (moderate risk FRAX, BMD T-score  $\geq -2.5$ , and no history of fragility fracture), what are the benefits and harms of stopping PTH analog (teriparatide or abaloparatide) treatment without starting a bisphosphonate/ denosumab/ or romosozumab versus stopping PTH analog and starting a bisphosphonate/denosumab/ or romosozumab to stabilize bone gains (though continuing calcium and vitamin D)?

**Summary:** The literature searched identified one randomized controlled by Bone et al. (2018) that reported on the findings of the ACTIVEExtend study. This study is an extension of the original ACTIVE trial (Miller et al. 2016) in which postmenopausal women with osteoporosis were randomized to abaloparatide (ABL, 80mcg daily), open label teriparatide (20mcg daily) or placebo (PBO) for 18 months. Following completion of the ACTIVE trial, there was an off-treatment period for a little over a month (described in Cosman et al. 2016), after which patients who were in the ABL group or the PBO group were re-enrolled in the ACTIVEExtend trial and received alendronate (ALN) for 24 months. Thus, there was an off-treatment period of up to 40 days, followed by 24 months on ALN, for a total of 43 months included in the integrated ACTIVE–ACTIVEExtend study period.

The original ACTIVE trial enrolled 2463 postmenopausal women with osteoporosis, aged 49 to 86 years. Women  $\leq 65$  years of age who had radiographic evidence of vertebral fracture at any time or who had a nonvertebral fracture within 5 years were eligible when they also had a BMD T-score of less than  $-2.5$  but greater than  $-5.0$  at the lumbar spine (LS) or femoral neck (FN). Women who were  $>65$  years of age who met these fracture criteria were allowed to enroll when their LS or FN BMD T-score was less than  $-2.0$  but greater than  $-5.0$ . Women older than 65 years could also enroll when their LS or FN BMD T-score was less than  $-3.0$  but greater than  $-5.0$ , even when they did not meet the fracture criteria. The ACTIVEExtend study enrolled 1,139 women, with 558 women transitioning from ABL to ALN (ABL/ALN) and 581 women transitioning to PBO/ALN. The primary outcome reported on in the ACTIVEExtend study was the proportion of patients with one or more incidents of vertebral fracture at the end of the study (at cumulative month 43). Other outcomes of interest reported included non-vertebral fracture, clinical fracture, and adverse events. The risk of bias for both studies was rated low due primarily to attrition ( $>20\%$  occurring during transition phases).

Low certainty of evidence suggests that patients who received 18 months of ABL followed by 24 months of ALN had fewer incidents of new radiographic vertebral fractures (primary outcome) compared to those who received 18 months of PBO followed by 24 months of ALN (0.9% vs 5.6%, RRR 84%). This represented a sustained reduction in radiographic vertebral fractures seen after the initial study. Low certainty of evidence also suggests that the incidence of non-vertebral fracture as well as major osteoporotic fracture were also lower in the ABL to ALN group

compared to PBO to ALN. The safety data presented only related to the open label extension period (ALN only) and was similar across the two groups.

- **Certainty of Evidence for the GIOP population: Very Low**

**TABLE 84. EVIDENCE AVAILABLE FOR ABALOPARATIDE TO BISPHOSPHONATE VS. PLACEBO TO BISPHOSPHONATE IN GENERAL POPULATION**

Certainty assessment							No of patients		Effect		Certainty	Importanc e
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABL to ALN	PBO to ALN	Relative (95% CI)	Absolute (95% CI)		
>/=1 new vertebral fracture 43 Months (Bone 2018)												
1	randomize d trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	5/558 (0.9%)	32/581 (5.5%)	Relative Risk 0.16 (0.06 to 0.41)	46 fewer per 1,000 (from 52 fewer to 32 fewer)	⊕⊕○○ Low	FAVORS ABL to ALN
Non-Vertebral Fracture 43 Months (Bone 2018)												
1	randomize d trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	27/55 8 (4.8%)	45/581 (7.7%)	Relative Risk 0.62 (0.39 to 0.99)	29 fewer per 1,000 (from 47 fewer to 1 fewer)	⊕⊕○○ Low	FAVORS ABL to ALN
Clinical Fracture 43 Months (Bone 2018)												
1	randomize d trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	38/55 8 (6.8%)	58/581 (10.0% )	Relative Risk 0.68 (0.46 to 1.01)	32 fewer per 1,000 (from 54 fewer to 1 more)	⊕○○○ Very Low	
Major Osteoporotic Fracture 43 Months (Bone 2018)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABL to ALN	PBO to ALN	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	not serious	none	20/558 (3.6%)	40/581 (6.9%)	<b>Relative Risk 0.52</b> (0.31 to 0.88)	<b>33 fewer per 1,000</b> (from 48 fewer to 8 fewer)	⊕⊕○○ Low	FAVORS ABL to ALN
<b>Hip Fracture 43 Months (Bone 2018)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	0/558 (0.0%)	3/581 (0.5%)	<b>Relative Risk 0.15</b> (0.01 to 2.87)	<b>4 fewer per 1,000</b> (from 5 fewer to 10 more)	⊕○○○ Very Low	
<b>&gt;/=1 Serious Treatment Emergent Adverse Event Months 19-43 (Bone 2018)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	65/553 (11.8%)	58/580 (10.0%)	<b>Relative Risk 1.18</b> (0.84 to 1.64)	<b>18 more per 1,000</b> (from 16 fewer to 64 more)	⊕○○○ Very Low	
<b>&gt;/=1 Serious Treatment Emergent Adverse Event Leading to Death Months 19-43 (Bone 2018)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	0/553 (0.0%)	2/580 (0.3%)	<b>Relative Risk 0.21</b> (0.01 to 4.36)	<b>3 fewer per 1,000</b> (from 3 fewer to 12 more)	⊕○○○ Very Low	
<b>Arthralgia Months 19-43 (Bone 2018)</b>												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ABL to ALN	PBO to ALN	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	54/553 (9.8%)	58/580 (10.0%)	<b>Relative Risk 0.98</b> (0.69 to 1.39)	<b>2 fewer per 1,000</b> (from 31 fewer to 39 more)	⊕○○○ Very Low	
<b>Upper Respiratory Track Infection Months 19-43 (Bone 2018)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	40/553 (7.2%)	51/580 (8.8%)	<b>Relative Risk 0.82</b> (0.55 to 1.22)	<b>16 fewer per 1,000</b> (from 40 fewer to 19 more)	⊕○○○ Very Low	
<b>Back Pain Months 19-43 (Bone 2018)</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	36/553 (6.5%)	34/580 (5.9%)	<b>Relative Risk 1.11</b> (0.71 to 1.75)	<b>6 more per 1,000</b> (from 17 fewer to 44 more)	⊕○○○ Very Low	

CI: confidence interval; RR: risk ratio

a. >20% drop out from start of ACTIVE to end of ACTIVEExtend

b. Population is post-menopausal osteoporosis, not GIOP (per protocol from ACTIVE study those on glucocorticoids within 12 months of screening were excluded)

c. Wide 95% confidence intervals

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## **MODERAT RISK**

**13.3.** For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral denosumab and are considered to have moderate fracture risk (moderate risk FRAX, BMD T-score  $\geq -2.5$ , and no history of fragility fracture), what are the benefits and harms of starting a bisphosphonate/ PTH analog/romosozumab when denosumab is discontinued versus not starting anti-osteoporosis medication when denosumab is discontinued (though continuing calcium and vitamin D)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**13.4.** For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral teriparatide (1-2years and are considered to have moderate fracture risk (moderate risk FRAX, BMD T-score  $\geq -2.5$ , and no history of fragility fracture), what are the benefits and harms of starting a bisphosphonate/ denosumab/romosozumab when PTH analog is discontinued versus not starting anti-osteoporosis medication when PTH analog is discontinued (though continuing calcium and vitamin D)?

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

## **HIGH RISK**

**13.5.** For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral denosumab, and are considered to have HIGH fracture risk (moderate risk FRAX, BMD T-score  $\geq -2.5$ , and history of fragility fracture), what are the benefits and harms of starting a bisphosphonate/romosozumab/PTH analog treatment when denosumab is discontinued versus not starting an anti-osteoporosis medication when denosumab is discontinued (though continuing calcium and vitamin D)



**Summary:** The ARCH trial assessed the transition of postmenopausal women with osteoporosis from 12 months of romosozumab (ROMO, 210 mg, monthly subcutaneous) or alendronate (ALN, 70 mg, orally every week) to an additional 12 months of alendronate (Saag et al. 2017). Overall, 2046 women transitioned from ROMO to ALN and 2047 transitions from ALN to ALN. Women in this study were randomized to initial treatment with ROMO or ALN. Only women with BMD T score of -2.5 or less at the total hip or femoral neck and either one or more moderate to severe vertebral fractures or two or more mild fractures were included. The primary outcomes, which were measured at 24 months, included fractures (vertebral, clinical, non-vertebral, hip), bone mineral density (lumbar spine, femoral neck, and total hip), and adverse events (osteonecrosis of the jaw, atypical femur fractures, and major adverse cardiovascular events). The table below presents the findings for fractures and adverse events. Evidence from this study is considered indirect primarily because the population in the study does not include patients with GIOP. Patients using glucocorticoids for >3 months at a prednisone equivalent dose of  $\geq 5.0$  mg/day were excluded from this study. All patients received daily calcium and vitamin D.

Low certainty of evidence suggests that 12 months of ROMO followed by 12 months of ALN compared to 24 months of ALN reduced vertebral, clinical, non-vertebral, and hip fractures. There was no difference in incidence of major adverse cardiovascular events. Few cases of osteonecrosis of the jaw or atypical femur fractures were reported.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

**TABLE 85. EVIDENCE AVAILABLE FOR TRANSITION FROM ROMOSOZUMAB TO ALENDRONATE IN THE GENERAL POPULATION**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROMO to ALN	ALN to ALN	Relative (95% CI)	Absolute (95% CI)		
new vertebral fracture, 24 mos												
1	randomized trials	serious <sup>a</sup>	Not serious	serious <sup>b</sup>	not serious	none	127/2046 (6.2%)	243/2047 (11.9%)	RR 0.52 (0.43 to 0.64)	57 fewer per 1,000 (from 68 fewer to 43 fewer)	⊕⊕○○ Low	Favors ROMO to ALN
clinical fracture, 24 mos												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROMO to ALN	ALN to ALN	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious <sup>a</sup>	Not serious	serious <sup>b</sup>	not serious	none	198/ 2046 (9.7%)	266/ 2047 (13.0%)	<b>RR 0.74</b> (0.63 to 0.89)	<b>34 fewer per 1,000</b> (from 48 fewer to 14 fewer)	⊕⊕○○ Low	Favors ROMO to ALN
<b>non-vertebral fracture, 24 mos</b>												
1	randomized trials	serious <sup>a</sup>	Not serious	serious <sup>b</sup>	not serious	none	178/ 2046 (8.7%)	217/ 2047 (10.6%)	<b>RR 0.82</b> (0.68 to 0.99)	<b>19 fewer per 1,000</b> (from 34 fewer to 1 fewer)	⊕⊕○○ Low	Favors ROMO to ALN
<b>Hip fracture, 24 mos</b>												
1	randomized trials	serious <sup>a</sup>	Not serious	serious <sup>b</sup>	not serious	none	41/ 2046 (2.0%)	66/ 2047 (3.2%)	<b>RR 0.62</b> (0.42 to 0.91)	<b>12 fewer per 1,000</b> (from 19 fewer to 3 fewer)	⊕⊕○○ Low	Favors ROMO to ALN
<b>osteonecrosis of the jaw</b>												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	1/2046 (0.0%)	1/ 2047 (0.0%)	<b>Relative Risk 1.00</b> (0.06 to 15.98)	<b>0 fewer per 1,000</b> (from 0 fewer to 7 more)	⊕○○○ Very Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROMO to ALN	ALN to ALN	Relative (95% CI)	Absolute (95% CI)		
atypical Femoral Fracture												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	2/2046 (0.1%)	4/2047 (0.2%)	Relative Risk 0.50 (0.09 to 2.73)	1 fewer per 1,000 (from 2 fewer to 3 more)	⊕○○○ Very Low	
serious Cardiovascular Event												
1	randomized trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	133/2046 (6.5%)	122/2047 (6.0%)	Relative Risk 1.09 (0.86 to 1.38)	5 more per 1,000 (from 8 fewer to 23 more)	⊕○○○ Very Low	

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

a. High risk of bias for open-label transition, unclear outcome assessor blinding, attrition >20%

b. Indirect population (not GIOP population)

c. Wide confidence interval

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**13.6.** For adults continuing chronic oral glucocorticoid treatment who have completed a full course of oral teriparatide (1-2years and are considered to have moderate fracture risk (moderate risk FRAX, BMD T-score  $\geq -2.5$ , and no history of fragility fracture), what are the benefits and harms of starting bisphosphonate/denosumab/ or romosozumab after stopping teriparatide versus not starting an anti-osteoporosis medication when denosumab is discontinued (though continuing calcium and vitamin D)

**Summary:** The literature searches did not identify any studies that addressed this PICO question.

- **Certainty of evidence across all critical outcomes for GIOP population: Very low**

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