SUPPLEMENTARY APPENDIX 3: Evidence Report/Summary of Findings/Recommendation

This document includes the original PICO questions (some were later combined or deleted due to lack of evidence, redundancy, or time during the voting session), the summary of evidence, and the strength of the recommendation. For PICO questions for which there was no evidence, there is a list of original algorithms that the Voting Panel used in decision making; some were changed during voting. At the end there is a more extensive list of the references for the trials cited in the evidence report.

Recommendation 1:
Treat all adults ≥ or < 40 taking prednisone at a dose of ≥ 2.5 mg for ≥ 3 months with Calcium and Vitamin D

Based on PICOs: 1.1a/b/c, 2.1, 3.1, 4.1a, 5.1, 6.1a, 6.1b, 1.2a/b/c, 2.2, 3.2, 4.2a, 5.2, 6.2a, 6.2b, 1.3a/b/c, 2.3, 3.3, 4.3a, 5.3, 6.3a, and 6.3b

PICO 1.1: In men and post-menopausal women ≥ age 40 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?

1.1a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D over No Supplementation with Calcium and Vitamin D

1.1b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D over No Supplementation with Calcium and Vitamin D

1.1c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D over No Supplementation with Calcium and Vitamin D

SUMMARY of FINDINGS

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 Participants (studies) Follow up	Quality 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 **36 months**	62 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.6** (0.16 to 2.3)	**161 per 1000**	**65 fewer per 1000** (from 135 fewer to 210 more)
Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 3** (0.14 to 63.15)	**0 per 1000**	**-**
Non-Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 0.33** (0.02 to 7.02)	**143 per 1000**	**96 fewer per 1000** (from 140 fewer to 860 more)
Serious Adverse Events	No data				
Total Adverse Events	No data				

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	43,324 (4 RCTs) 2 to 7 years	⨁⨁⨁⨀ **MODERATE**	**RR 0.98** (0.77 to 1.25)	**11 per 1000** Over a mean of 4.5 years	**0 fewer per 1000** (from 3 fewer to 3 more)
Vertebral Fracture	42,115 (3 RCTs) 3 to 7 years	⨁⨁⨁⨀ **MODERATE**	**RR 0.90** (0.74 to 1.09)	**10 per 1000** Over a mean of 5 years	**1 fewer per 1000** (from 3 fewer to 1 more)

Non-Vertebral Fracture	5,833 (2 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.93** (0.78 to 1.09)	**88 per 1000** Over a mean of 5 years	**6 fewer per 1000** (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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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] Outcome is only addressed by one study
[3] Very small sample size at the time point measured.
[4] Received "high risk of bias" rating in 5/7 categories.
[5] Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

PICO 2.1: In adults < age 40 with 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?

Recommendation: The recommendation from PICO 1.1c was applied due to absence of evidence specific to this population.

SUMMARY of FINDINGS

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 Participants (studies)** Follow up	**Quality 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 **36 months**	62 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.6** (0.16 to 2.3)	**161 per 1000**	**65 fewer per 1000** (from 135 fewer to 210 more)
Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 3** (0.14 to 63.15)	**0 per 1000**	**-**
Non-Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 0.33** (0.02 to 7.02)	**143 per 1000**	**96 fewer per 1000** (from 140 fewer to 860 more)
Serious Adverse Events	No data				
Total Adverse Events	No data				

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	43,324 (4 RCTs) 2 to 7 years	⨁⨁⨁⨀ **MODERATE**	**RR 0.98** (0.77 to 1.25)	**11 per 1000** Over a mean of 4.5 years	**0 fewer per 1000** (from 3 fewer to 3 more)
Vertebral Fracture	42,115 (3 RCTs) 3 to 7 years	⨁⨁⨁⨀ **MODERATE**	**RR 0.90** (0.74 to 1.09)	**10 per 1000** Over a mean of 5 years	**1 fewer per 1000** (from 3 fewer to 1 more)

Non-Vertebral Fracture	5,833 (2 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.93** (0.78 to 1.09)	**88 per 1000** Over a mean of 5 years	**6 fewer per 1000** (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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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] Outcome is only addressed by one study
[3] Very small sample size at the time point measured.
[4] Received "high risk of bias" rating in 5/7 categories.
[5] Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

PICO 3.1: 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?

Recommendation: The recommendation from PICO 1.1b was applied due to absence of evidence specific to this population.

SUMMARY of FINDINGS

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 Participants (studies) Follow up	Quality 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 **36 months**	62 (1 RCT) 36 months	⨁⨁⊖⊖ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.6** (0.16 to 2.3)	**161 per 1000**	**65 fewer per 1000** (from 135 fewer to 210 more)

Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 3** (0.14 to 63.15)	**0 per 1000**	-
Non-Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 0.33** (0.02 to 7.02)	**143 per 1000**	**96 fewer per 1000** (from 140 fewer to 860 more)
Serious Adverse Events			No data		
Total Adverse Events			No data		

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	43,324 (4 RCTs) 2 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.98** (0.77 to 1.25)	**11 per 1000** Over a mean of 4.5 years	**0 fewer per 1000** (from 3 fewer to 3 more)
Vertebral Fracture	42,115 (3 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.90** (0.74 to 1.09)	**10 per 1000** Over a mean of 5 years	**1 fewer per 1000** (from 3 fewer to 1 more)
Non-Vertebral Fracture	5,833 (2 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.93** (0.78 to 1.09)	**88 per 1000** Over a mean of 5 years	**6 fewer per 1000** (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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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] Outcome is only addressed by one study
[3] Very small sample size at the time point measured.
[4] Received "high risk of bias" rating in 5/7 categories.
[5] Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

PICO 4.1a: In adults < age 40 without past fragility fracture and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are thebenefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

Recommendation: The recommendation from PICO 1.1a was applied due to absence of evidence specific to this population.

SUMMARY of FINDINGS

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 Participants (studies) Follow up	Quality 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 **36 months**	62 (1 RCT) 36 months	⨁⨁⊖⊖ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.6** (0.16 to 2.3)	**161 per 1000**	**65 fewer per 1000** (from 135 fewer to 210 more)
Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 3** (0.14 to 63.15)	**0 per 1000**	**-**
Non-	14	⨁⊖⊖⊖	**RR 0.33**	**143 per 1000**	**96 fewer per 1000**

Vertebral Fracture **6 months**	(1 RCT) 6 months	**VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	(0.02 to 7.02)		(from 140 fewer to 860 more)
Serious Adverse Events			No data		
Total Adverse Events			No data		

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	43,324 (4 RCTs) 2 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.98** (0.77 to 1.25)	**11 per 1000** Over a mean of 4.5 years	**0 fewer per 1000** (from 3 fewer to 3 more)
Vertebral Fracture	42,115 (3 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.90** (0.74 to 1.09)	**10 per 1000** Over a mean of 5 years	**1 fewer per 1000** (from 3 fewer to 1 more)
Non-Vertebral Fracture	5,833 (2 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.93** (0.78 to 1.09)	**88 per 1000** Over a mean of 5 years	**6 fewer per 1000** (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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are uncertain about the estimate.

[1] 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] Outcome is only addressed by one study
[3] Very small sample size at the time point measured.
[4] Received "high risk of bias" rating in 5/7 categories.
[5] Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

PICO 5.1: 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 calcium and vitamin D versus treatment with no calcium or vitamin D?

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

SUMMARY of FINDINGS

Evidence Available for Non-Renal Transplant Patients:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for Renal Transplant Recipients:

Outcomes	No of Participants (studies) Follow up	Quality 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**[1,2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 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**[1,3,5,6] 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**[1,3,6] due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months	
Hypercalcaemia **6 months**	111 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 2.12** (0.45 to 10.05)	**43 per 1000**	**49 more per 1000** (from 24 fewer to 393 more)
Hypercalcaemia **12 months**	51 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[3,4,5,7] due to risk of bias, imprecision	**RR 3.85** (0.9 to 16.38)	**80 per 1000**	**228 more per 1000** (from 8 fewer to 1000 more)
Transplant Rejection	111 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,5] due to risk of bias, indirectness, imprecision	**RR 0.97** (0.49 to 1.91)	**239 per 1000**	**7 fewer per 1000** (from 122 fewer to 218 more)
Death	111 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,5,6] due to risk of bias, indirectness, imprecision	Not estimable	No incidence of Death in either group over 6 months	

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† [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† [10]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	43,324 (4 RCTs) 2 to 7 years	⊕⊕⊕⊖ **MODERATE**	**RR 0.98** (0.77 to 1.25)	**11 per 1000** Over a mean of 4.5 years	**0 fewer per 1000** (from 3 fewer to 3 more)
Vertebral Fracture	42,115 (3 RCTs) 3 to 7 years	⊕⊕⊕⊖ **MODERATE**	**RR 0.90** (0.74 to 1.09)	**10 per 1000** Over a mean of 5 years	**1 fewer per 1000** (from 3 fewer to 1 more)
Non-Vertebral Fracture	5,833 (2 RCTs) 3 to 7 years	⊕⊕⊕⊖ **MODERATE**	**RR 0.93** (0.78 to 1.09)	**88 per 1000** Over a mean of 5 years	**6 fewer per 1000** (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]

GRADE Working Group grades of evidence

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

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

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

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

[1] Open label trial(s)
[2] Outcomes assessed at time points <1 year were agreed to be indirect
[3] Small sample size
[4] 95% CI is (are) wide
[5] Outcome only assessed by one study
[6] Due to zero events, effect of at least one trial is inestimable
[7] Over 20% discontinuation in one or both groups

PICO 6.1a: For adults age ≥ 30 years receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone with cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

Recommendation: The recommendations from PICOs 2.1 and 3.1 were applied due to absence of evidence specific to this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

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 Participants (studies) Follow up	Quality 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 **36 months**	62 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.6** (0.16 to 2.3)	**161 per 1000**	**65 fewer per 1000** (from 135 fewer to 210 more)
Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 3** (0.14 to 63.15)	**0 per 1000**	**-**
Non-Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 0.33** (0.02 to 7.02)	**143 per 1000**	**96 fewer per 1000** (from 140 fewer to 860 more)
Serious Adverse Events			No data		
Total Adverse Events			No data		

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;

Evidence Available for General Osteoporosis Population:

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

				Calcium and Vitamin D*	with Calcium and Vitamin D (95% CI)**
Hip Fracture	43,324 (4 RCTs) 2 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.98** (0.77 to 1.25)	**11 per 1000** Over a mean of 4.5 years	**0 fewer per 1000** (from 3 fewer to 3 more)
Vertebral Fracture	42,115 (3 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.90** (0.74 to 1.09)	**10 per 1000** Over a mean of 5 years	**1 fewer per 1000** (from 3 fewer to 1 more)
Non-Vertebral Fracture	5,833 (2 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.93** (0.78 to 1.09)	**88 per 1000** Over a mean of 5 years	**6 fewer per 1000** (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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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] Outcome is only addressed by one study

[3] Very small sample size at the time point measured.

[4] Received "high risk of bias" rating in 5/7 categories.

[5] Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

PICO 6.1b: For adults aged <30 years receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg/d and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with calcium and vitamin D versus treatment with no calcium or vitamin D?

Recommendation: The recommendations from PICOs 2.1 and 3.1 were applied due to absence of

evidence specific to this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for GIOP Population:

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 Participants (studies) Follow up	Quality 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)**
Hip Fracture			No data		

Vertebral Fracture **36 months**	62 (1 RCT) 36 months	⨁⨁⊖⊖ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.6** (0.16 to 2.3)	**161 per 1000**	**65 fewer per 1000** (from 135 fewer to 210 more)
Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 3** (0.14 to 63.15)	**0 per 1000**	**-**
Non-Vertebral Fracture **6 months**	14 (1 RCT) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3,4,5] due to risk of bias, indirectness, imprecision	**RR 0.33** (0.02 to 7.02)	**143 per 1000**	**96 fewer per 1000** (from 140 fewer to 860 more)
Serious Adverse Events			No data		
Total Adverse Events			No data		

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;

Evidence Available for General Osteoporosis Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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)**
Hip Fracture	43,324 (4 RCTs) 2 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.98** (0.77 to 1.25)	**11 per 1000** Over a mean of 4.5 years	**0 fewer per 1000** (from 3 fewer to 3 more)
Vertebral Fracture	42,115 (3 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.90** (0.74 to 1.09)	**10 per 1000** Over a mean of 5	**1 fewer per 1000** (from 3 fewer to 1 more)

				years	
Non-Vertebral Fracture	5,833 (2 RCTs) 3 to 7 years	⨁⨁⨁⊖ **MODERATE**	**RR 0.93** (0.78 to 1.09)	**88 per 1000** Over a mean of 5 years	**6 fewer per 1000** (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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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] Outcome is only addressed by one study
[3] Very small sample size at the time point measured.
[4] Received "high risk of bias" rating in 5/7 categories.
[5] Outcome assessed at 6 months. We agreed any study not reporting 12 months or beyond would be downgraded for indirectness.

PICO 1.2: In men and post-menopausal women ≥ age 40 and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications alone versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

1.2a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D over Lifestyle Modifications alone

1.2b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D over Lifestyle Modifications alone

1.2c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D over Lifestyle Modifications alone

PICO 2.2: In adults < age 40 with past fragility fracture and continuing/beginning chronic oral glucocorticoid treatment, what are the benefits and harms of treatment with lifestyle modifications alone versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.2c was applied due to absence of evidence specific to this population.

PICO 3.2: 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.2b was applied due to absence of evidence specific to this population.

PICO 4.2a: In adults < age 40 without past fragility fracture 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.2a was applied due to absence of evidence specific to this population.

PICO 5.2: 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 lifestyle modifications versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 6.2a: For adults ≥ age 30 receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: The recommendations from PICOs 2.2 and 3.2 were applied due to absence of evidence specific to this population.

PICO 6.2b: For adults < age 30 receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with lifestyle modifications versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: The recommendations from PICOs 2.2 and 3.2 were applied due to absence of evidence specific to this population.

PICO 1.3: In men and post-menopausal women ≥ age 40 and 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?

This PICO was not directly addressed by any studies.

1.3a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D in addition to Lifestyle Modifications over Supplementation with Calcium and Vitamin D alone

1.3b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D in addition to Lifestyle Modifications over Supplementation with Calcium and Vitamin D alone

1.3c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D in addition to Lifestyle Modifications over Supplementation with Calcium and Vitamin D alone

PICO 2.3: In adults < age 40 with 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.3c was applied due to absence of evidence specific to this population.

PICO 3.3: 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.3b was applied due to absence of evidence specific to this population.

PICO 4.3a: In adults < age 40 without past fragility fracture 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.3a was applied due to absence of evidence specific to this population.

PICO 5.3: 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 lifestyle modifications, calcium, and vitamin D versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 6.3a: For adults ≥ 30 receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendations from PICOs 2.3 and 3.3 were applied due to absence of evidence specific to this population

PICO 6.3b: For adults < age 30 receiving receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone with cumulative dose > 5 grams over one year), 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendations from PICOs 2.3 and 3.3 were applied due to absence of evidence specific to this population

Recommendations 2, 3, and 4:
In Low Risk patients, Treat with Calcium and Vitamin D and lifestyle modifications over treatment with bisphosphonates, teriparatide, denosumab, and raloxifene with Calcium and Vitamin D

In Moderate and High risk patients, Treat with Oral Bisphosphonate and Calcium and Vitamin D over Calcium and Vitamin D alone, IV Bisphosphonates, Teriparatide, Denosumab, and Raloxifene

Based on PICOs: 1.4a/b/c, 1.5a/b/c, 1.6a/b/c, 1.7a/b/c, 1.8a/b/c, 1.9a/b/c, 1.10a/b/c, 1.11a/b/c, 1.12a/b/c, 1.13a/b/c, 1.14a/b/c, 1.15a/b/c, 1.16a/b/c, 1.17a/b/c, 1.18a/b/c

PICO 1.4: In men and post-menopausal women ≥ age 40 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?

1.4a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Conditionally in favor of Calcium and Vitamin D alone over Oral Bisphosphonate + Calcium and Vitamin D

1.4b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D alone

1.4c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Strongly in favor of Oral Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

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

Outcomes	No of Participants (studies) Follow up	Quality 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 **12 months**	532 (5 RCTs) 12 months	⨁⨁◯◯ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.57** (0.09 to 3.56)	**9 per 1000**	**4 fewer per 1000** (from 8 fewer to 22 more)
Vertebral	202 (1 RCT)	⨁⨁◯◯ **LOW**[4,5]	**RR 0.1** (0.01 to	**68 per 1000**	**61 fewer per 1000** (from 7 fewer to 67 fewer)

Fracture **24 months**	24 months	due to risk of bias, imprecision	0.9)		
Vertebral Fracture **12 months**	1051 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[2,3,6] due to risk of bias, imprecision	**RR 0.66** (0.25 to 1.77)	**69 per 1000**	**23 fewer per 1000** (from 52 fewer to 53 more)
Non-Vertebral Fracture **24 months**	208 (1 RCT) 24 months	⨁⨁⨀⨀ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.55** (0.2 to 1.53)	**98 per 1000**	**44 fewer per 1000** (from 79 fewer to 52 more)
Non-Vertebral Fracture **12 months**	1353 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[3,7,8] due to risk of bias, imprecision	**RR 0.89** (0.52 to 1.53)	**43 per 1000**	**5 fewer per 1000** (from 21 fewer to 23 more)
Serious Adverse Events	1192 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[2,3,7] due to risk of bias, imprecision	**RR 0.95** (0.76 to 1.18)	**213 per 1000**	**11 fewer per 1000** (from 51 fewer to 38 more)
Total Adverse Events	848 (6 RCTs) 12 months	⨁⨁⨁⨀ **MODERATE**[7] due to risk of bias	**RR 0.97** (0.9 to 1.05)	**753 per 1000**	**23 fewer per 1000** (from 75 fewer to 38 more)
Upper GI Adverse Events	996 (4 RCTs) 12 months	⨁⨁⨁⨀ **MODERATE**[7] due to risk of bias	**RR 1.14** (0.88 to 1.48)	**184 per 1000**	**26 more per 1000** (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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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**	**RR 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	22,022	⨁⨁⨁⨁	**RR 0.84**	**106 per 1000**	**17 fewer per 1000**

Fracture	(2 meta-analyses) **HIGH** 1 to 4 years	(0.77 to 0.91)	Over a mean of 2.5 years	(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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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
[2] 3 studies had effects with wide 95% CI.
[3] The effect of at least one study is inestimable due to zero events
[4] Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.
[5] Outcome is only assessed by one study
[6] 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.
[7] More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.
[8] 4 studies have very wide 95% CI

PICO 1.5: In men and post-menopausal women ≥ age 40 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?

1.5a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Strongly in favor of Calcium and Vitamin D alone over IV Bisphosphonate + Calcium and Vitamin D

1.5b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D alone

1.5c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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 [23]; Lyles, et al., N Engl J Med. 2007; 357(18):1799-809 [24].

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 1.6: In post-menopausal women ≥ age 40 and 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?

1.6a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Strongly in favor of Calcium and Vitamin D alone over Raloxifene + Calcium and Vitamin D

1.6b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Calcium and Vitamin D alone over Raloxifene + Calcium and Vitamin D

1.6c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Raloxifene + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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)	⨁⨁◯◯ **LOW**[1,2,3,4]	**RR 0.16** (0.01 to 2.96)	**54 per 1000**	**45 fewer per 1000**

	12 months	due to imprecision			(from 53 fewer to 105 more)
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events	114 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[2,4] due to imprecision	**RR 0.88** (0.47 to 1.62)	**281 per 1000**	**34 fewer per 1000** (from 149 fewer to 174 more)

Bibliography: Mok, et al. Ann Rheum Dis. 2011 May; 70(5): 778-84 [25]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	10,101 (1 RCT) 5.6 years	⊕⊕⊕⊕ **HIGH**	**RR 0.86** (0.65 to 1.15)	**7 per 1000** Over 3 years	**1 fewer per 1000** (from 2 fewer to 1 more)
Vertebral Fracture	5,600 (1 meta- analysis) 1 to 3 years	⊕⊕⊕⊕ **HIGH**	**RR 0.60** (0.49 to 0.74)	**101 per 1000** Over 3 years	**40 fewer per 1000** (from 26 fewer to 52 fewer)
Non-Vertebral Fracture	13,835 (2 RCTs) 3 to 5.6 years	⊕⊕⊕⊕ **HIGH**	**RR 0.80** (0.51 to 1.25)	**93 per 1000** Over 3 years	**19 fewer per 1000** (from 46 fewer to 23 more)

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the

estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Noted uneven distribution of discontinuations; very low discontinuation rate overall.
[2] Outcome only assessed by one study
[3] 95% CI is wide
[4] Very small sample size
[5]Control event rates were not available

PICO 1.7: In men and post-menopausal women ≥ age 40 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?

1.7a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Conditionally in favor of Calcium and Vitamin D alone over Teriparatide + Calcium and Vitamin D

1.7b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Calcium and Vitamin D alone

1.7c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Calcium and Vitamin D alone*	**Risk difference with Teriparatide** (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		

Serious Adverse Events	No data
Total Adverse Events	No data
Bibliography: NA	

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;

Evidence Available for General Osteoporosis Population:

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

Bibliography: Crandall, et al. AHRQ CER 53, March 2012; Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 1.8: In men and post-menopausal women ≥ 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 calcium and vitamin D?

1.8a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: Conditionally in favor of Calcium and Vitamin D alone over Denosumab + Calcium and Vitamin D

1.8b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Calcium and Vitamin D alone

1.8c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⨁⨀ **MODERATE**[1] due to imprecision	**RR 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	⨁⨁⨁⨁ **HIGH**	**RR 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	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	**RR 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; 1 2: 209;[23] Bone, et al. J Clin Endocrinol Metab. 2008; 93 (6):2149-57 [32]; Cummings, et al. N Engl J Med. 2009 Aug 20; 361 (8):756-65 [33]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is only assessed by one study

[2] 95% CI of one trial passes beyond the other and passes null effect

PICO 1.9: In men and post-menopausal women ≥ age 40 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?

1.9a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.9a because a treatment option was eliminated in a previous PICO question

1.9b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.9b because a treatment option was eliminated in a previous PICO question

1.9c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over IV Bisphosphonate + Calcium and Vitamin D

SUMMARY of FINDINGS

Bibliography: Reid, et al. Lancet. 2009 Apr 11; 373(9671): 1253-63 [34]

Outcomes	No of Participants (studies) Follow up	Quality 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**[1,2,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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 [34]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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: Crandall, et al. AHRQ CER 53, March 2012; Tauchmanovà, 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome only assessed by one study

[2] 95% CI is wide and crosses null effect

[3] Per Panel Request, Reid 2009 was downgraded from an original grade of "Moderate" to a new grade of "Low" (5/14/16)

PICO 1.10: In post-menopausal women ≥ age 40 and continuing/beginning 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?

1.10a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.10a because a treatment option was eliminated in a previous PICO question

1.10b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.10b because a treatment option was eliminated in a previous PICO question

1.10c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Strongly in favor of Oral Bisphosphonate + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Oral Bisphosphonate*	**Risk difference with Raloxifene** (95% CI)**
Hip Fracture	No data				
Vertebral Fracture	No data				
Non-Vertebral Fracture	No data				
Serious Adverse Events	No data				
Total Adverse Events	No data				
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Oral Bisphosphonate*	**Risk difference with Raloxifene** (95% CI)**
Hip Fracture	1,412 (1 RCT) 2 years	⨁⨁⊖⊖ **LOW**	**RR 2.04** (0.19 to 22.45)	**1 per 1000** Over 2 years	**1 more per 1000** (from 1 fewer to 30 more)

Vertebral Fracture	514 (1 RCT) 2 years	⨁⨁⨀⨀ **LOW**	**RR 0.62** (0.20 to 1.86)	**31 per 1000** Over 2 years	**12 fewer per 1000** (from 25 fewer to 27 more)
Non-Vertebral Fracture	1,412 (1 RCT) 2 years	⨁⨁⨀⨀ **LOW**	**RR 1.09** (0.53 to 2.25)	**20 per 1000** Over 2 years	**2 more per 1000** (from 9 fewer to 25 more)

Bibliography: Recker, et al. Bone. 2007 Apr;40(4):843-51 [37]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 1.11: In men and post-menopausal women ≥ age 40 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?

1.11a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.11a because a treatment option was eliminated in a previous PICO question

1.11b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

1.11c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

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]

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
Hip Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 8.14)	**5 per 1000**	**3 fewer per 1000** (from 5 fewer to 33 more)
Vertebral Fracture **36 months**	342 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 0.23** (0.07 to 0.78)	**77 per 1000**	**59 fewer per 1000** (from 17 fewer to 72 fewer)
Vertebral Fracture **18 months**	336 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,5] due to imprecision	**RR 0.1** (0.01 to 0.75)	**61 per 1000**	**55 fewer per 1000** (from 15 fewer to 60 fewer)
Non-Vertebral Fracture **36 months**	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to risk of bias, imprecision	**RR 1.07** (0.54 to 2.1)	**70 per 1000**	**5 more per 1000** (from 32 fewer to 77 more)
Non-Vertebral Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to imprecision	**RR 1.5** (0.63 to 3.6)	**37 per 1000**	**19 more per 1000** (from 14 fewer to 97 more)
Serious Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.06** (0.87 to 1.28)	**299 per 1000**	**18 more per 1000** (from 39 fewer to 84 more)
Total Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.05** (0.98 to 1.13)	**860 per 1000**	**43 more per 1000** (from 17 fewer to 112 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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 0.30** (0.09 to 1.05)	**137 per 1000** Over 1 year	**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 [40]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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.

[2] Outcome only assessed by one study

[3] 95% CI is wide

[4] 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.

[5] 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)

PICO 1.12: In men and post-menopausal women ≥ 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 oral bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

1.12a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.12a because a treatment option was eliminated in a previous PICO question

1.12b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

1.12c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 1.13: In post-menopausal women ≥ age 40 and continuing/beginning 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?

This PICO was not directly addressed by any studies.

1.13a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.13a because a treatment option was eliminated in a previous PICO question

1.13b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.13b because a treatment option was eliminated in a previous PICO question

1.13c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

PICO 1.14: In men and post-menopausal women ≥ age 40 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?

This PICO was not directly addressed by any studies.

1.14a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.14a because a treatment option was eliminated in a previous PICO question

1.14b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.14b because a treatment option was eliminated in a previous PICO question

1.14c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

PICO 1.15: In men and post-menopausal women ≥ 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 IV bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

1.15a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.15a because a treatment option was eliminated in a previous PICO question

1.15b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.15b because a treatment option was eliminated in a previous PICO question

1.15c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 1.16: In post-menopausal women ≥ age 40 and 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?

This PICO was not directly addressed by any studies.

1.16a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.16a because a treatment option was eliminated in a previous PICO question

1.16b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.16b because a treatment option was eliminated in a previous PICO question

1.16c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

PICO 1.17: In post-menopausal women ≥ 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 raloxifene, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

1.17a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.17a because a treatment option was eliminated in a previous PICO question

1.17b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.17b because a treatment option was eliminated in a previous PICO question

1.17c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

PICO 1.18: In men and post-menopausal women ≥ 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?

This PICO was not directly addressed by any studies.

1.18a Low risk (Baseline risk assessment by FRAX= <10% for Major OP fracture, <2% for hip fracture)

Recommendation: No recommendation was made for PICO 1.18a because a treatment option was eliminated in a previous PICO question

1.18b Moderate risk (Baseline risk assessment by FRAX= 10-19% for Major OP fracture, 2% for hip fracture)

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

1.18c High Risk (Past fragility fracture, BMD T score < -2.5 at the hip or spine, and/or baseline risk assessment by FRAX ≥ 20% for Major OP fracture, ≥3% for hip fracture)

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

Recommendation 5:
Treat adults < age 40 at Low Risk of Fracture with Calcium and Vitamin D and Lifestyle modifications over treatment with Bisphosphonates, Teriparatide, or Denosumab with Calcium and Vitamin D

Based on PICOs: 4.4a, 4.5a, 4.6a, 4.7a, 4.8a, 4.9a, 4.10a, 4.11a, 4.12a, and 4.13a

PICO 4.4a: In adults < age 40 without past fragility fracture 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?

Recommendation: The recommendation from PICO 1.4a was applied due to absence of evidence specific to this population.

SUMMARY of FINDINGS

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

Outcomes	No of Participants (studies) Follow up	Quality 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 **12 months**	532 (5 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.57** (0.09 to 3.56)	**9 per 1000**	**4 fewer per 1000** (from 8 fewer to 22 more)
Vertebral Fracture **24 months**	202 (1 RCT) 24 months	⨁⨁⨀⨀ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.1** (0.01 to 0.9)	**68 per 1000**	**61 fewer per 1000** (from 7 fewer to 67 fewer)
Vertebral Fracture **12 months**	1051 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[2,3,6] due to risk of bias, imprecision	**RR 0.66** (0.25 to 1.77)	**69 per 1000**	**23 fewer per 1000** (from 52 fewer to 53 more)
Non-Vertebral Fracture **24 months**	208 (1 RCT) 24 months	⨁⨁⨀⨀ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.55** (0.2 to 1.53)	**98 per 1000**	**44 fewer per 1000** (from 79 fewer to 52 more)
Non-Vertebral Fracture **12 months**	1353 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[3,7,8] due to risk of bias, imprecision	**RR 0.89** (0.52 to 1.53)	**43 per 1000**	**5 fewer per 1000** (from 21 fewer to 23 more)
Serious Adverse	1192 (7 RCTs)	⨁⨁⨀⨀ **LOW**[2,3,7]	**RR 0.95** (0.76 to 1.18)	**213 per 1000**	**11 fewer per 1000** (from 51 fewer to 38

Events	12 months	due to risk of bias, imprecision			more)
Total Adverse Events	848 (6 RCTs) 12 months	⨁⨁⨁⊖ **MODERATE**[7] due to risk of bias	**RR 0.97** (0.9 to 1.05)	**753 per 1000**	**23 fewer per 1000** (from 75 fewer to 38 more)
Upper GI Adverse Events	996 (4 RCTs) 12 months	⨁⨁⨁⊖ **MODERATE**[7] due to risk of bias	**RR 1.14** (0.88 to 1.48)	**184 per 1000**	**26 more per 1000** (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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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**	**RR 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**	**RR 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.[21]; Cochrane Database Syst Rev. 2008 Jan 23; (1):CD004523 [22]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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
[2] 3 studies had effects with wide 95% CI.
[3] The effect of at least one study is inestimable due to zero events
[4] Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

[5] Outcome is only assessed by one study
[6] 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.
[7] More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.
[8] 4 studies have very wide 95% CI

PICO 4.5a: In adults < age 40 without past fragility fracture and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are thebenefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: The recommendation from PICO 1.5a was applied due to absence of evidence specific to this population

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⨁⊖ **MODERATE**	**RR 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	⨁⨁⨁⊖ **MODERATE**	**RR 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	⨁⨁⨁⊖ **MODERATE**	**RR 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 [23]; Lyles, et al., N Engl J Med. 2007; 357(18):1799-809 [24].

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 4.6a: In adults < age 40 without past fragility fracture 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?

Recommendation: The recommendation from PICO 1.7a was applied due to absence of evidence specific to this population

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Teriparatide (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

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

Bibliography: Crandall, et al. AHRQ CER 53, March 2012; Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 4.7a: In adults < age 40 without past fragility fracture and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are thebenefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: The recommendation from PICO 1.8a was applied due to absence of evidence specific

to this population

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⨁⊖ **MODERATE**[1] due to imprecision	**RR 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	⨁⨁⨁⨁ **HIGH**	**RR 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	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 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; 1 2: 209;[23] Bone, et al. J Clin Endocrinol Metab. 2008; 93 (6):2149-57 [32]; Cummings, et al. N Engl J Med. 2009 Aug 20; 361 (8):756-65 [33]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is only assessed by one study

[2] 95% CI of one trial passes beyond the other and passes null effect

PICO 4.8a: In adults < age 40 without past fragility fracture and without BMD Z score < -3 at hip or spine and continuing/beginning chronic oral glucocorticoid treatment, what are thebenefits and harms of treatment with IV bisphosphonate, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

Recommendation: The recommendation from PICO 1.9a was applied due to absence of evidence specific to this population

SUMMARY of FINDINGS

Bibliography: Reid, et al. Lancet. 2009 Apr 11; 373(9671): 1253-63 [34]

Outcomes	No of Participants (studies) Follow up	Quality 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**[1,2,3] due to imprecision	**RR 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)	⨁⨁⊖⊖ **LOW**[1,3]	**RR 0.99** (0.74 to 1.32)	**185 per 1000**	**2 fewer per 1000**

	12 months	due to imprecision			(from 48 fewer to 59 more)
Total Adverse Events	833 (1 RCT) 12 months	⨁⨁⊖⊖ **LOW**[1,3] due to imprecision	**RR 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 [34]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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: Crandall, et al. AHRQ CER 53, March 2012; Tauchmanovà, 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome only assessed by one study

[2] 95% CI is wide and crosses null effect

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

PICO 4.9a: In adults < age 40 without past fragility fracture and without BMD Z score < -3 at hip or

spine and continuing/beginning chronic oral glucocorticoid treatment, what are thebenefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

Recommendation: The recommendation from PICO 1.11a was applied due to absence of evidence specific to this population

SUMMARY of FINDINGS

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]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate *	Risk difference with Teriparatide (95% CI)**
Hip Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 8.14)	**5 per 1000**	**3 fewer per 1000** (from 5 fewer to 33 more)
Vertebral Fracture **36 months**	342 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 0.23** (0.07 to 0.78)	**77 per 1000**	**59 fewer per 1000** (from 17 fewer to 72 fewer)
Vertebral Fracture **18 months**	336 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,5] due to imprecision	**RR 0.1** (0.01 to 0.75)	**61 per 1000**	**55 fewer per 1000** (from 15 fewer to 60 fewer)
Non-Vertebral Fracture **36 months**	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to risk of bias, imprecision	**RR 1.07** (0.54 to 2.1)	**70 per 1000**	**5 more per 1000** (from 32 fewer to 77 more)
Non-Vertebral Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to imprecision	**RR 1.5** (0.63 to 3.6)	**37 per 1000**	**19 more per 1000** (from 14 fewer to 97 more)
Serious Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.06** (0.87 to 1.28)	**299 per 1000**	**18 more per 1000** (from 39 fewer to 84 more)
Total Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.05** (0.98 to 1.13)	**860 per 1000**	**43 more per 1000** (from 17 fewer to 112 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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 0.30** (0.09 to 1.05)	**137 per 1000** Over 1 year	**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 [40]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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.

[2] Outcome only assessed by one study

[3] 95% CI is wide

[4] 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.

[5] 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)

PICO 4.10a: In adults < age 40 without past fragility fracture 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.12a was applied due to absence of evidence specific to this population.

PICO 4.11a: In adults < age 40 without past fragility fracture 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.14a was applied due to absence of evidence specific to this population

PICO 4.12a: In adults < age 40 without past fragility fracture 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.15a was applied due to absence of evidence specific to this population.

PICO 4.13a: In adults < age 40 without past fragility fracture 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.18a was applied due to absence of evidence specific to this population.

Recommendation 6:
Treat adults < 40 at Moderate to High Risk of fracture with Oral Bisphosphonates and Calcium and Vitamin D over Calcium and Vitamin D alone or with IV Bisphosphonates, Teriparatide, and Denosumab

Based on PICOs: 2.4, 3.4, 4.1b, 2.5, 3.5, 4.2b, 2.6, 3.6, 4.4b, 2.7, 3.7, 4.5b, 2.8, 3.8, 4.3b, 2.9, 3.9, 2.10, 3.10, 2.11, 3.11, 2.12, 3.12, 2.13, and 3.13

PICO 2.4: In adults < age 40 with 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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D

SUMMARY of FINDINGS

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

Outcomes	No of Participants (studies) Follow up	Quality 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 **12 months**	532 (5 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.57** (0.09 to 3.56)	**9 per 1000**	**4 fewer per 1000** (from 8 fewer to 22 more)
Vertebral Fracture **24 months**	202 (1 RCT) 24 months	⨁⨁⨀⨀ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.1** (0.01 to 0.9)	**68 per 1000**	**61 fewer per 1000** (from 7 fewer to 67 fewer)
Vertebral Fracture **12 months**	1051 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[2,3,6] due to risk of bias, imprecision	**RR 0.66** (0.25 to 1.77)	**69 per 1000**	**23 fewer per 1000** (from 52 fewer to 53 more)
Non-Vertebral Fracture **24 months**	208 (1 RCT) 24 months	⨁⨁⨀⨀ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.55** (0.2 to 1.53)	**98 per 1000**	**44 fewer per 1000** (from 79 fewer to 52 more)
Non-Vertebral Fracture **12 months**	1353 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[3,7,8] due to risk of bias, imprecision	**RR 0.89** (0.52 to 1.53)	**43 per 1000**	**5 fewer per 1000** (from 21 fewer to 23 more)

Serious Adverse Events	1192 (7 RCTs) 12 months	⊕⊕⊖⊖ **LOW**[2,3,7] due to risk of bias, imprecision	**RR 0.95** (0.76 to 1.18)	**213 per 1000**	**11 fewer per 1000** (from 51 fewer to 38 more)
Total Adverse Events	848 (6 RCTs) 12 months	⊕⊕⊕⊖ **MODERATE**[7] due to risk of bias	**RR 0.97** (0.9 to 1.05)	**753 per 1000**	**23 fewer per 1000** (from 75 fewer to 38 more)
Upper GI Adverse Events	996 (4 RCTs) 12 months	⊕⊕⊕⊖ **MODERATE**[7] due to risk of bias	**RR 1.14** (0.88 to 1.48)	**184 per 1000**	**26 more per 1000** (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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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**	**RR 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**	**RR 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 [21]; Cochrane Database Syst Rev. 2008 Jan 23; (1):CD004523 [22]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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
[2] 3 studies had effects with wide 95% CI.
[3] The effect of at least one study is inestimable due to zero events
[4] Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.
[5] Outcome is only assessed by one study
[6] 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.
[7] More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.
[8] 4 studies have very wide 95% CI

PICO 3.4: 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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D

SUMMARY of FINDINGS

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

Outcomes	No of Participants (studies) Follow up	Quality 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 **12 months**	532 (5 RCTs) 12 months	⨁⨁◯◯ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.57** (0.09 to 3.56)	**9 per 1000**	**4 fewer per 1000** (from 8 fewer to 22 more)
Vertebral Fracture **24 months**	202 (1 RCT) 24 months	⨁⨁◯◯ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.1** (0.01 to 0.9)	**68 per 1000**	**61 fewer per 1000** (from 7 fewer to 67 fewer)
Vertebral Fracture **12 months**	1051 (7 RCTs) 12 months	⨁⨁◯◯ **LOW**[2,3,6] due to risk of bias, imprecision	**RR 0.66** (0.25 to 1.77)	**69 per 1000**	**23 fewer per 1000** (from 52 fewer to 53 more)
Non-Vertebral	208	⨁⨁◯◯	**RR 0.55**	**98 per 1000**	**44 fewer per 1000**

Fracture **24 months**	(1 RCT) 24 months	**LOW**[4,5] due to risk of bias, imprecision	(0.2 to 1.53)		(from 79 fewer to 52 more)
Non-Vertebral Fracture **12 months**	1353 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[3,7,8] due to risk of bias, imprecision	**RR 0.89** (0.52 to 1.53)	**43 per 1000**	**5 fewer per 1000** (from 21 fewer to 23 more)
Serious Adverse Events	1192 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[2,3,7] due to risk of bias, imprecision	**RR 0.95** (0.76 to 1.18)	**213 per 1000**	**11 fewer per 1000** (from 51 fewer to 38 more)
Total Adverse Events	848 (6 RCTs) 12 months	⨁⨁⨁⨀ **MODERATE**[7] due to risk of bias	**RR 0.97** (0.9 to 1.05)	**753 per 1000**	**23 fewer per 1000** (from 75 fewer to 38 more)
Upper GI Adverse Events	996 (4 RCTs) 12 months	⨁⨁⨁⨀ **MODERATE**[7] due to risk of bias	**RR 1.14** (0.88 to 1.48)	**184 per 1000**	**26 more per 1000** (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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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**	**RR 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**	**RR 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.[21]; Cochrane Database Syst Rev. 2008 Jan 23; (1):CD004523 [22]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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
[2] 3 studies had effects with wide 95% CI.
[3] The effect of at least one study is inestimable due to zero events
[4] Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.
[5] Outcome is only assessed by one study
[6] 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.
[7] More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.
[8] 4 studies have very wide 95% CI

PICO 4.1b: In adults < age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a significant 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.4b was applied due to absence of evidence specific to this population

PICO 2.5: In adults < age 40 with 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 calcium and vitamin D?

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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 [23]; Lyles, et al., N Engl J Med. 2007; 357(18):1799-809 [24].

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 3.5: 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?

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⨁⨀ **MODERATE**	**RR 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	⨁⨁⨁⨀ **MODERATE**	**RR 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	⨁⨁⨁⨀ **MODERATE**	**RR 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 [23]; Lyles, et al., N Engl J Med. 2007; 357(18):1799-809 [24].

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 4.2b: In adults < age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a significant 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.5b was applied due to absence of evidence specific to this population

PICO 2.6: In adults < age 40 with 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?

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Calcium and Vitamin D alone*	**Risk difference with Teriparatide** (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

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

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

Bibliography: Crandall, et al. AHRQ CER 53, March 2012; Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 3.6: 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 calcium and vitamin D?

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D alone*	Risk difference with Teriparatide (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse			No data		

Events	
Total Adverse Events	No data
Bibliography: NA	

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;

Evidence Available for General Osteoporosis Population:

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

Bibliography: Crandall, et al. AHRQ CER 53, March 2012; Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 4.4b: In adults < age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a significant 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.7b was applied due to absence of evidence specific to this population.

PICO 2.7: In adults < age 40 with 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?

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

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

				Vitamin D alone*	Denosumab (95% CI)**
Hip Fracture	7,297 (1 RCT) 3 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 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	⊕⊕⊕⊕ **HIGH**	**RR 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	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	**RR 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; 1 2: 209;[23] Bone, et al. J Clin Endocrinol Metab. 2008; 93 (6):2149-57 [32]; Cummings, et al. N Engl J Med. 2009 Aug 20; 361 (8):756-65 [33]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is only assessed by one study

[2] 95% CI of one trial passes beyond the other and passes null effect

PICO 3.7: 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?

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Calcium and Vitamin D alone

SUMMARY of FINDINGS

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		

Vertebral Fracture	No data
Non-Vertebral Fracture	No data
Serious Adverse Events	No data
Total Adverse Events	No data
Bibliography: NA	

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 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	⊕⊕⊕⊕ **HIGH**	**RR 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	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	**RR 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; 1 2: 209;[23] Bone, et al. J Clin Endocrinol Metab. 2008; 93 (6):2149-57 [32]; Cummings, et al. N Engl J Med. 2009 Aug 20; 361 (8):756-65 [33]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is only assessed by one study

[2] 95% CI of one trial passes beyond the other and passes null effect

PICO 4.5b: In adults < age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a significant 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.8b was applied due to absence of evidence specific to this population.

PICO 2.8: In adults < age 40 with 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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over IV Bisphosphonate + Calcium and Vitamin D

SUMMARY of FINDINGS

Bibliography: Reid, et al. Lancet. 2009 Apr 11; 373(9671): 1253-63 [34]

Outcomes	No of Participants (studies) Follow up	Quality 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**[1,2,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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 [34]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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: Crandall, et al. AHRQ CER 53, March 2012; Tauchmanovà, 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome only assessed by one study

[2] 95% CI is wide and crosses null effect

[3] Per Panel Request, Reid 2009 was downgraded from an original grade of "Moderate" to a new grade of "Low" (5/14/16)

PICO 3.8: 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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over IV Bisphosphonate + Calcium and Vitamin D

SUMMARY of FINDINGS

Bibliography: Reid, et al. Lancet. 2009 Apr 11; 373(9671): 1253-63 [34]

Outcomes	**No of Participants (studies)** Follow up	**Quality 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**[1,2,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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 [34]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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: Crandall, et al. AHRQ CER 53, March 2012; Tauchmanovà, 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

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

[1] Outcome only assessed by one study

[2] 95% CI is wide and crosses null effect

[3] Per Panel Request, Reid 2009 was downgraded from an original grade of "Moderate" to a new grade of "Low" (5/14/16)

PICO 4.3b: In adults < age 40 with neither prior fracture nor BMD Z score < -3 at hip or spine but with a significant 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?

This PICO was not directly addressed by any studies.

Recommendation: The recommendation from PICO 1.9b was applied due to absence of evidence specific to this population.

PICO 2.9: In adults < age 40 with 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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

SUMMARY of FINDINGS

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]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
Hip Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁◯◯ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 8.14)	**5 per 1000**	**3 fewer per 1000** (from 5 fewer to 33 more)
Vertebral Fracture **36 months**	342 (1 RCT) 36 months	⨁⨁◯◯ **LOW**[2,4,5] due to imprecision	**RR 0.23** (0.07 to 0.78)	**77 per 1000**	**59 fewer per 1000** (from 17 fewer to 72 fewer)
Vertebral Fracture **18 months**	336 (1 RCT) 18 months	⨁⨁◯◯ **LOW**[1,2,5] due to imprecision	**RR 0.1** (0.01 to 0.75)	**61 per 1000**	**55 fewer per 1000** (from 15 fewer to 60 fewer)

Non-Vertebral Fracture **36 months**	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to risk of bias, imprecision	**RR 1.07** (0.54 to 2.1)	**70 per 1000**	**5 more per 1000** (from 32 fewer to 77 more)
Non-Vertebral Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to imprecision	**RR 1.5** (0.63 to 3.6)	**37 per 1000**	**19 more per 1000** (from 14 fewer to 97 more)
Serious Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.06** (0.87 to 1.28)	**299 per 1000**	**18 more per 1000** (from 39 fewer to 84 more)
Total Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.05** (0.98 to 1.13)	**860 per 1000**	**43 more per 1000** (from 17 fewer to 112 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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 0.30** (0.09 to 1.05)	**137 per 1000** Over 1 year	**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 [40]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

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

[1] 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.
[2] Outcome only assessed by one study
[3] 95% CI is wide
[4] 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.
[5] 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)

PICO 3.9: 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 thebenefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

SUMMARY of FINDINGS

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]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate *	Risk difference with Teriparatide (95% CI)**
Hip Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁◯◯ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 8.14)	**5 per 1000**	**3 fewer per 1000** (from 5 fewer to 33 more)
Vertebral Fracture **36 months**	342 (1 RCT) 36 months	⨁⨁◯◯ **LOW**[2,4,5] due to imprecision	**RR 0.23** (0.07 to 0.78)	**77 per 1000**	**59 fewer per 1000** (from 17 fewer to 72 fewer)
Vertebral Fracture **18 months**	336 (1 RCT) 18 months	⨁⨁◯◯ **LOW**[1,2,5] due to imprecision	**RR 0.1** (0.01 to 0.75)	**61 per 1000**	**55 fewer per 1000** (from 15 fewer to 60 fewer)

Non-Vertebral Fracture **36 months**	428 (1 RCT) 36 months	⊕⊕⊖⊖ **LOW**[2,4,5] due to risk of bias, imprecision	**RR 1.07** (0.54 to 2.1)	**70 per 1000**	**5 more per 1000** (from 32 fewer to 77 more)
Non-Vertebral Fracture **18 months**	428 (1 RCT) 18 months	⊕⊕⊖⊖ **LOW**[1,2,3,5] due to imprecision	**RR 1.5** (0.63 to 3.6)	**37 per 1000**	**19 more per 1000** (from 14 fewer to 97 more)
Serious Adverse Events	428 (1 RCT) 36 months	⊕⊕⊖⊖ **LOW**[2,4,5] due to imprecision	**RR 1.06** (0.87 to 1.28)	**299 per 1000**	**18 more per 1000** (from 39 fewer to 84 more)
Total Adverse Events	428 (1 RCT) 36 months	⊕⊕⊖⊖ **LOW**[2,4,5] due to imprecision	**RR 1.05** (0.98 to 1.13)	**860 per 1000**	**43 more per 1000** (from 17 fewer to 112 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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 0.30** (0.09 to 1.05)	**137 per 1000** Over 1 year	**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 [40]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the

estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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.
[2] Outcome only assessed by one study
[3] 95% CI is wide
[4] 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.
[5] 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)

PICO 2.10: In adults < age 40 with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 3.10: 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 thebenefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 2.11: In adults < age 40 with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

PICO 3.11: 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 thebenefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

PICO 2.12: In adults < age 40 with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 3.12: 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 2.13: In adults < age 40 with 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 ?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 3.13: 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

Recommendation 7:
In Women of childbearing potential at moderate to high risk of fracture who do not plan to become pregnant within the period of osteoporosis treatment and are using effective birth control or are not sexually active, Treat with Oral Bisphosphonate and Calcium and Vitamin D over Calcium and Vitamin D alone or with Teriparatide, IV Bisphosphonates, or Denosumab

Based on PICOs: 2.4cbp, 3.4cbp, 6.4b.cbp, 2.5cbp, 3.5cbp, 6.5b.cbp, 2.6cbp, 3.6cbp, 6.6b.cbp, 2.7cbp, 3.7cbp, 6.7b.cbp, 2.8cbp, 3.8cbp, 6.8b.cbp, 2.9cbp, 3.9cbp, 2.10cbp, 3.10cbp, 2.11cbp, 3.11cbp, 2.12cbp, 3.12cbp, 2.13cbp, and 3.13cbp

PICO 2.4 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D

PICO 3.4 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D

PICO 6.4.b.cbp: For women of childbearing potential receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 2.5 cbp: In women of childbearing potential with 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 calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D

PICO 3.5 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D

PICO 6.5.b.cbp: For women of childbearing potential receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 2.6 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Calcium and Vitamin D

PICO 3.6 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Calcium and Vitamin D

PICO 6.6.b.cbp: For women of childbearing potential receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 2.7 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Calcium and Vitamin D

PICO 3.7 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Calcium and Vitamin D

PICO 6.7.b.cbp: For women of childbearing potential very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 2.8 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over IV Bisphosphonate + Calcium and Vitamin D

PICO 3.8 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over IV Bisphosphonate + Calcium and Vitamin D

PICO 6.8.b.cbp: For women of childbearing potential receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 2.9 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

PICO 2.10 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: Strongly in favor of Oral Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 3.10 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: Strongly in favor of Oral Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 2.11 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

PICO 3.11 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

PICO 2.12 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: No recommendation was made for PICO 2.12 because a treatment option was eliminated in a previous PICO question

PICO 3.12 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: No recommendation was made for PICO 3.12 because a treatment option was eliminated in a previous PICO question

PICO 2.13 cbp: In women of childbearing potential with 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?

This PICO was not directly addressed by any studies.

Recommendation: No recommendation was made for PICO 2.13 because a treatment option was eliminated in a previous PICO question

PICO 3.13 cbp: In women of childbearing potential 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?

This PICO was not directly addressed by any studies.

Recommendation: No recommendation was made for PICO 3.13 because a treatment option was eliminated in a previous PICO question

Recommendation 8:
In Adults ≥ age 30 receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year)), Treat with an Oral Bisphosphonate and Calcium and Vitamin D over Calcium and Vitamin D alone

Based on PICOs: 6.4a, 6.5a, 6.6a, 6.7a, 6.8a, 6.9a, 6.10a, 6.11a, 6.12a, 6.13a, 6.14a, 6.16a, 6.17a, 6.18a

PICO 6.4a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: Conditionally in favor of Oral Bisphosphonates + Calcium and Vitamin D over Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	72 (1 RCT) 18 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 7.92)	**28 per 1000**	**19 fewer per 1000** (from 28 fewer to 192 more)
Vertebral Fracture	109 (2 RCTs) 18 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,6] due to risk of bias, imprecision	**RR 0.13** (0.01 to 2.25)	**71 per 1000**	**62 fewer per 1000** (from 71 fewer to 89 more)
Non-Vertebral Fracture	72 (1 RCT) 18 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 7.92)	**28 per 1000**	**19 fewer per 1000** (from 28 fewer to 192 more)

Bibliography: Okada, et al. J Rheumatol. 2008 Nov;35(11):2249-54 [16]; Saadati, 2008 [17]

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;

Evidence Available for GIOP Population:

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

Outcomes	No of Participants	Quality of the	Relative	Anticipated absolute effects

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

Evidence Available for General Osteoporosis Population:

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

				Vitamin D alone*	(95% CI)**
Hip Fracture	21,811 (2 meta-analyses) 1 to 4 years	⊕⊕⊕⊕ **HIGH**	**RR 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**	**RR 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**	**RR 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. [21]; Cochrane Database Syst Rev. 2008 Jan 23; (1):CD004523 [22]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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

[2] 3 studies had effects with very wide 95% CI.

[3] The effect of at least one study is inestimable due to zero events

[4] Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

[5] Outcome is only assessed by one study

[6] Small sample size

[7] 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.

[8] More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

[9] 4 studies have very wide 95% CI

PICO 6.5a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: Conditionally in favor of IV Bisphosphonates + Calcium and Vitamin D over Calcium

and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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 [23]; Lyles, et al., N Engl J Med. 2007; 357(18):1799-809 [24].

GRADE Working Group grades of evidence

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

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

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

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

PICO 6.6a: For post-menopausal women receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with raloxifene, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: Conditionally in favor of Raloxifene + Calcium and Vitamin D over Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⊖⊖ **LOW**[1,2,3,4] due to imprecision	**RR 0.16** (0.01 to 2.96)	**54 per 1000**	**45 fewer per 1000** (from 53 fewer to 105 more)
Non-Vertebral Fracture			No data		

Serious Adverse Events		No data			
Total Adverse Events	114 (1 RCT) 12 months	⨁⨁⊖⊖ **LOW**[2,4] due to imprecision	**RR 0.88** (0.47 to 1.62)	**281 per 1000**	**34 fewer per 1000** (from 149 fewer to 174 more)

Bibliography: Mok, et al. Ann Rheum Dis. 2011 May; 70(5): 778-84 [25]

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;

Evidence Available for General Osteoporosis Population:

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

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Noted uneven distribution of discontinuations; very low discontinuation rate overall.

[2] Outcome only assessed by one study

[3] 95% CI is wide

[4] Very small sample size

[5]Control event rates were not available

PICO 6.7a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Calcium and Vitamin D alone*	**Risk difference with Teriparatide** (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Calcium and Vitamin D alone*	**Risk difference with Teriparatide** (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		

Total Adverse Events	No data

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

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

Bibliography: Crandall, et al. AHRQ CER 53, March 2012; Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 6.8a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 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	⊕⊕⊕⊕ **HIGH**	**RR 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	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	**RR 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; 1 2: 209;[23] Bone, et al. J Clin Endocrinol Metab. 2008; 93 (6):2149-57 [32]; Cummings, et al. N Engl J Med. 2009 Aug 20; 361 (8):756-65 [33]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is only assessed by one study

[2] 95% CI of one trial passes beyond the other and passes null effect

PICO 6.9a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over IV Bisphosphonate + Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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**[1,2,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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 [34]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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: Crandall, et al. AHRQ CER 53, March 2012; Tauchmanovà, 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]

GRADE Working Group grades of evidence

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

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

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

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

[1] Outcome only assessed by one study

[2] 95% CI is wide and crosses null effect

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

PICO 6.10a: For post-menopausal women receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are thebenefits and harms of treatment with raloxifene, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Raloxifene (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

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

Non-Vertebral Fracture	No data
Serious Adverse Events	No data
Total Adverse Events	No data

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	**Risk difference with Raloxifene** (95% CI)**
Hip Fracture	1,412 (1 RCT) 2 years	⊕⊕⊖⊖ **LOW**	**RR 2.04** (0.19 to 22.45)	**1 per 1000** Over 2 years	**1 more per 1000** (from 1 fewer to 30 more)
Vertebral Fracture	514 (1 RCT) 2 years	⊕⊕⊖⊖ **LOW**	**RR 0.62** (0.20 to 1.86)	**31 per 1000** Over 2 years	**12 fewer per 1000** (from 25 fewer to 27 more)
Non-Vertebral Fracture	1,412 (1 RCT) 2 years	⊕⊕⊖⊖ **LOW**	**RR 1.09** (0.53 to 2.25)	**20 per 1000** Over 2 years	**2 more per 1000** (from 9 fewer to 25 more)

Bibliography: Recker, et al. Bone. 2007 Apr;40(4):843-51 [37]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 6.11a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
Hip Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁◯◯ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 8.14)	**5 per 1000**	**3 fewer per 1000** (from 5 fewer to 33 more)
Vertebral	342 (1 RCT)	⨁⨁◯◯ **LOW**[2,4,5]	**RR 0.23** (0.07 to	**77 per 1000**	**59 fewer per 1000** (from 17 fewer to

Fracture **36 months**	36 months	due to imprecision	0.78)		72 fewer)
Vertebral Fracture **18 months**	336 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,5] due to imprecision	**RR 0.1** (0.01 to 0.75)	**61 per 1000**	**55 fewer per 1000** (from 15 fewer to 60 fewer)
Non-Vertebral Fracture **36 months**	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to risk of bias, imprecision	**RR 1.07** (0.54 to 2.1)	**70 per 1000**	**5 more per 1000** (from 32 fewer to 77 more)
Non-Vertebral Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to imprecision	**RR 1.5** (0.63 to 3.6)	**37 per 1000**	**19 more per 1000** (from 14 fewer to 97 more)
Serious Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.06** (0.87 to 1.28)	**299 per 1000**	**18 more per 1000** (from 39 fewer to 84 more)
Total Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.05** (0.98 to 1.13)	**860 per 1000**	**43 more per 1000** (from 17 fewer to 112 more)

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]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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	146 (1 RCT)	⨁⨁⨀⨀ **LOW**	**RR 0.30** (0.09 to 1.05)	**137 per 1000** Over 1 year	**96 fewer per 1000** (from

Fracture	1 year		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 [40]

GRADE Working Group grades of evidence

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

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

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

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

[1] 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.

[2] Outcome only assessed by one study

[3] 95% CI is wide

[4] 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.

[5] 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)

PICO 6.12a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 6.13a: For post-menopausal women receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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 ?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

PICO 6.14a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5s 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Teriparatide + Calcium and Vitamin D

PICO 6.15a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

PICO 6.16a: For post-menopausal women receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are thebenefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with raloxifene, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

PICO 6.17a: For post-menopausal women receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are thebenefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with raloxifene, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Denosumab + Calcium and Vitamin D over Raloxifene + Calcium and Vitamin D

PICO 6.18a: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Teriparatide + Calcium and Vitamin D over Denosumab + Calcium and Vitamin D

No Recommendations were made for Adults < age 30 receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone with cumulative dose > 5 grams over one year)

Based on PICOs: 6.4b, 6.5b, 6.6b, 6.7b, 6.8b, 6.9b, 6.10b, 6.11b, 6.12b, and 6.13b

PICO 6.4b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	72 (1 RCT) 18 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 7.92)	**28 per 1000**	**19 fewer per 1000** (from 28 fewer to 192 more)
Vertebral Fracture	109 (2 RCTs) 18 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,6] due to risk of bias, imprecision	**RR 0.13** (0.01 to 2.25)	**71 per 1000**	**62 fewer per 1000** (from 71 fewer to 89 more)
Non-Vertebral Fracture	72 (1 RCT) 18 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 7.92)	**28 per 1000**	**19 fewer per 1000** (from 28 fewer to 192 more)

Bibliography: Okada, et al. J Rheumatol. 2008 Nov;35(11):2249-54 [16]; Saadati, et al. Iranian Red Crescent Medical Journal 2008.1 (2008): 8-11 [17]

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;

Evidence Available for GIOP Population:

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

Outcomes	No of Participants (studies) Follow up	Quality 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 **12 months**	532 (5 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.57** (0.09 to 3.56)	**9 per 1000**	**4 fewer per 1000** (from 8 fewer to 22 more)
Vertebral Fracture **24 months**	202 (1 RCT) 24 months	⨁⨁⨀⨀ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.1** (0.01 to 0.9)	**68 per 1000**	**61 fewer per 1000** (from 7 fewer to 67 fewer)
Vertebral Fracture **12 months**	1051 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[2,3,6] due to risk of bias, imprecision	**RR 0.66** (0.25 to 1.77)	**69 per 1000**	**23 fewer per 1000** (from 52 fewer to 53 more)
Non-Vertebral Fracture **24 months**	208 (1 RCT) 24 months	⨁⨁⨀⨀ **LOW**[4,5] due to risk of bias, imprecision	**RR 0.55** (0.2 to 1.53)	**98 per 1000**	**44 fewer per 1000** (from 79 fewer to 52 more)
Non-Vertebral Fracture **12 months**	1353 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[3,7,8] due to risk of bias, imprecision	**RR 0.89** (0.52 to 1.53)	**43 per 1000**	**5 fewer per 1000** (from 21 fewer to 23 more)
Serious Adverse Events	1192 (7 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[2,3,7] due to risk of bias, imprecision	**RR 0.95** (0.76 to 1.18)	**213 per 1000**	**11 fewer per 1000** (from 51 fewer to 38 more)
Total Adverse Events	848 (6 RCTs) 12 months	⨁⨁⨁⨀ **MODERATE**[7] due to risk of bias	**RR 0.97** (0.9 to 1.05)	**753 per 1000**	**23 fewer per 1000** (from 75 fewer to 38 more)
Upper GI Adverse Events	996 (4 RCTs) 12 months	⨁⨁⨁⨀ **MODERATE**[7] due to risk of bias	**RR 1.14** (0.88 to 1.48)	**184 per 1000**	**26 more per 1000** (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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants	Quality of the evidence	Relative effect (95% CI)	Anticipated absolute effects

	(studies) Follow up	(GRADE)		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**	**RR 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**	**RR 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**	**RR 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. [21]; Cochrane Database Syst Rev. 2008 Jan 23; (1):CD004523 [22]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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

[2] 3 studies had effects with very wide 95% CI.

[3] The effect of at least one study is inestimable due to zero events

[4] Adachi 2001: Randomization and blinding procedures and discontinuations were not clearly described.

[5] Outcome is only assessed by one study

[6] Small sample size

[7] 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.

[8] More than half of studies had high discontinuation rates, did not describe discontinuation adequately, or showed evidence of differential discontinuation between groups.

[9] 4 studies have very wide 95% CI

PICO 6.5b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		

Total Adverse Events	No data

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⨁⊖ **MODERATE**	**RR 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	⨁⨁⨁⊖ **MODERATE**	**RR 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	⨁⨁⨁⊖ **MODERATE**	**RR 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 [23]; Lyles, et al., N Engl J Med. 2007; 357(18):1799-809 [24].

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 6.6b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Calcium and Vitamin D alone*	**Risk difference with Teriparatide** (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for GIOP Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Calcium and Vitamin D alone*	**Risk difference with Teriparatide** (95% CI)**
Hip Fracture			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;
Evidence Available for General Osteoporosis Population:

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

Bibliography: Crandall, et al. AHRQ CER 53, March 2012; Hopkins, et al. BMC Musculoskelet Disord. 2011 Sep 26; 1 2: 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]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 6.7b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams over one year), what are the benefits and harms of treatment with denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Vertebral Fracture			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 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	⊕⊕⊕⊕ **HIGH**	**RR 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	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	**RR 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; 1 2: 209;[23] Bone, et al. J Clin Endocrinol Metab. 2008; 93 (6):2149-57 [32]; Cummings, et al. N Engl J Med. 2009 Aug 20; 361 (8):756-65 [33]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PICO 6.8b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Non-Vertebral Fracture			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**[1,2,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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**[1,3] due to imprecision	**RR 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 [34]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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: Crandall, et al. AHRQ CER 53, March 2012; Tauchmanovà, 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]

GRADE Working Group grades of evidence

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

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

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

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

[1] Outcome only assessed by one study

[2] 95% CI is wide and crosses null effect

[3] Per Panel Request, Reid 2009 was downgraded from an original grade of "Moderate" to a new grade of "Low" (5/14/16)

PICO 6.9b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

SUMMARY of FINDINGS

Evidence Available for High Dose Steroid Population:

Outcomes	**No of Participants (studies)** Follow up	**Quality 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			No data		
Serious Adverse Events			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for GIOP Population:

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral Bisphosphonate*	Risk difference with Teriparatide (95% CI)**
Hip Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 0.33** (0.01 to 8.14)	**5 per 1000**	**3 fewer per 1000** (from 5 fewer to 33 more)
Vertebral Fracture **36 months**	342 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 0.23** (0.07 to 0.78)	**77 per 1000**	**59 fewer per 1000** (from 17 fewer to 72 fewer)
Vertebral Fracture **18 months**	336 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,5] due to imprecision	**RR 0.1** (0.01 to 0.75)	**61 per 1000**	**55 fewer per 1000** (from 15 fewer to 60 fewer)
Non-Vertebral Fracture **36 months**	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to risk of bias, imprecision	**RR 1.07** (0.54 to 2.1)	**70 per 1000**	**5 more per 1000** (from 32 fewer to 77 more)
Non-Vertebral Fracture **18 months**	428 (1 RCT) 18 months	⨁⨁⨀⨀ **LOW**[1,2,3,5] due to imprecision	**RR 1.5** (0.63 to 3.6)	**37 per 1000**	**19 more per 1000** (from 14 fewer to 97 more)
Serious Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.06** (0.87 to 1.28)	**299 per 1000**	**18 more per 1000** (from 39 fewer to 84 more)
Total Adverse Events	428 (1 RCT) 36 months	⨁⨁⨀⨀ **LOW**[2,4,5] due to imprecision	**RR 1.05** (0.98 to 1.13)	**860 per 1000**	**43 more per 1000** (from 17 fewer to 112 more)

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]

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 0.30** (0.09 to 1.05)	**137 per 1000** Over 1 year	**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 [40]

GRADE Working Group grades of evidence

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

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

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

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

[1] 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.

[2] Outcome only assessed by one study

[3] 95% CI is wide

[4] 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.

[5] 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)

PICO 6.10b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 6.11b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 6.12b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

PICO 6.13b: For adults receiving very high dose glucocorticoid therapy (starting dose ≥ 30 mg prednisone and cumulative dose > 5 grams 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?

This PICO was not directly addressed by any studies.

Recommendation: The consensus was that there was insufficient data to recommend treatment in this population.

Recommendation 9:
Treat adults with organ transplant, GFR ≥ 30 mL/min, and no evidence of metabolic bone disease who are continuing treatment with glucocorticoids, according to the age-related guidelines for adults without transplants with these additional recommendations

Based on PICOs: 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 5.16, 5.17, 5.18, 5.19, and 5.20

PICO 5.4: 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 oral bisphosphonate, calcium, and vitamin D versus treatment with calcium and vitamin D?

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

SUMMARY of FINDINGS

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	Quality 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 **24 months**	92 (1 RCT) 24 months	⨁⨁◯◯ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.47** (0.13 to 1.7)	**146 per 1000**	**77 fewer per 1000** (from 127 fewer to 102 more)
Vertebral fracture **12 months**	181 (2 RCTs) 12 months	⨁⨁◯◯ **LOW**[1,3,4] due to risk of bias, imprecision	**RR 0.43** (0.16 to 1.17)	**130 per 1000**	**74 fewer per 1000** (from 110 fewer to 22 more)
Non-Vertebral Fracture **24 months**	92 (1 RCT) 24 months	⨁⨁◯◯ **LOW**[1,2,3,4] due to risk of bias, imprecision	**RR 0.22** (0.01 to 4.41)	**42 per 1000**	**33 fewer per 1000** (from 41 fewer to 142 more)
Non-Vertebral	181 (2 RCTs)	⨁⨁◯◯ **LOW**[1,3,4,5]	**RR 0.36** (0.02 to	**11 per 1000**	**7 fewer per 1000** (from 11 fewer to

Fracture **12 months**	12 months	due to risk of bias, imprecision	8.68)		83 more)
Death	187 (2 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[1,3,4] due to risk of bias, imprecision	**RR 1.97** (0.51 to 7.61)	**32 per 1000**	**31 more per 1000** (from 16 fewer to 213 more)
Transplant Rejection	89 (1 RCT) 12 months	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.61** (0.31 to 1.2)	**364 per 1000**	**142 fewer per 1000** (from 251 fewer to 73 more)
GI Adverse Events	89 (1 RCT) 12 months	⨁⨁⨀⨀ **LOW**[1,2,3,4] due to risk of bias, imprecision	**RR 2.61** (0.74 to 9.19)	**68 per 1000**	**110 more per 1000** (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;

[1] Open label trial(s)
[2] Outcome only assessed by one study
[3] Small sample size
[4] 95% CI of at least one study is wide
[5] Due to zero events, effect of one trial is inestimable

Evidence Available for Renal Transplant Recipients:

Bibliography: Giannini, et al. J Bone Miner Res. 2001 Nov; 16(11): 2111-7† [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† [46]

Outcomes	No of Participants (studies) Follow up	Quality 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 **12 months**	164 (3 RCTs) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	Not estimable	No incidence of Hip Fracture in either group over 12 months. Effect not estimable.	
Vertebral Fracture **12 months**	245 (4 RCTs) 12 months	⊕⊕⊖⊖ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.72** (0.29 to 1.82)	**79 per 1000**	**22 fewer per 1000** (from 56 fewer to 65 more)
Non-Vertebral Fracture **12 months**	119 (2 RCTs) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months. Effect not estimable.	
Total Adverse Events	101 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,4,5] due to risk of bias, imprecision	**RR 0.77** (0.47 to 1.25)	**449 per 1000**	**103 fewer per 1000** (from 238 fewer to 112 more)
Gastrointestinal Adverse Events	40 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,4,5] due to risk of bias, imprecision	**RR 1** (0.29 to 3.45)	**200 per 1000**	**0 fewer per 1000** (from 142 fewer to 490 more)
Transplant Rejection	223 (3 RCTs) 12 months	⊕⊕⊖⊖ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 1.26** (0.3 to 5.33)	**26 per 1000**	**7 more per 1000** (from 18 fewer to 113 more)
Death	185 (2 RCTs) 12 months	⊕⊕⊖⊖ **LOW**[1,2,3,5] due to risk of bias, imprecision	**RR 0.31** (0.01 to 7.54)	**11 per 1000**	**7 fewer per 1000** (from 11 fewer to 70 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).

†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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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**	**RR 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**	**RR 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.[21]; Cochrane Database Syst Rev. 2008 Jan 23; (1):CD004523 [22]

GRADE Working Group grades of evidence

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

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

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

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

[1] Majority of studies assessing this outcome were open label

[2] Due to zero events, the effect of at least one study was inestimable.

[3] 95% CI of trials are wide

[4] Outcome only assessed by one study

[5] Small sample size

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?

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

SUMMARY of FINDINGS

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	Quality 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 **24 months**	154 (2 RCTs) 24 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 0.36** (0.14 to 0.93)	**188 per 1000**	**120 fewer per 1000** (from 13 fewer to 161 fewer)
Vertebral Fracture **12 months**	94 (2 RCTs) 12 months	⊕⊕⊖⊖ **LOW**[2,3] due to risk of bias, imprecision	**RR 0.24** (0.07 to 0.83)	**234 per 1000**	**178 fewer per 1000** (from 40 fewer to 218 fewer)
Non-Vertebral Fracture **24 months**	58 (1 RCT) 24 years	⊕⊖⊖⊖ **VERY LOW**[4,5,6] due to risk of bias, imprecision	**RR 0.29** (0.03 to 2.41)	**129 per 1000**	**92 fewer per 1000** (from 125 fewer to 182 more)
Non-Vertebral Fracture **12 months**	62 (1 RCT) 12 months	⊕⊕⊕⊖ **MODERATE**[5,6] due to imprecision	**RR 1.88** (0.18 to 19.63)	**33 per 1000**	**29 more per 1000** (from 27 fewer to 621 more)
Transplant Rejection	96 (1 RCT) 24 months	⊕⊕⊖⊖ **LOW**[5,6,7] due to risk of bias, imprecision	**RR 1.46** (0.63 to 2.95)	**122 per 1000**	**56 more per 1000** (from 45 fewer to 239 more)
Hypocalcaemia	96 (1 RCT)	⊕⊕⊖⊖ **LOW**[5,6,7]	**RR 3.65** (0.8 to	**41 per 1000**	**108 more per 1000** (from 8 fewer to 640 more)

24 months	24 months	due to risk of bias, imprecision	16.68)		
Hypocalcaemia **12 months**	62 (1 RCT) 12 months	⨁⨁⊖⊖ **LOW** [5,6,7] due to risk of bias, imprecision	**RR 4.06** (1.28 to 12.86)	**100 per 1000**	**306 more per 1000** (from 28 more 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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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.
[2] Both trials have small sample size. 95% CI of one trial is wide and crosses null effect.
[3] Inconsistencies in reporting in one of the included trials.
[4] OPEN LABEL trial. Rated "high risk of bias" in 5/7 categories. Evidence of differential baseline characteristics between groups.
[5] Outcome only assessed by one study
[6] 95% CI is wide; very small sample size
[7] OPEN label trial

Evidence Available for Renal Transplant Recipients:

Bibliography: Smerud, et al. Am J Transplant. 2012 Dec;12(12): 3316-25 † [51]

Outcomes	**No of Participants (studies)** Follow up	**Quality 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 **12 months**	129 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,2,3] due to imprecision	**RR 1.91** (0.17 to 16.42)	**16 per 1000**	**14 more per 1000** (from 13 fewer to 245 more)
Non-Vertebral Fracture			No data		
Serious Adverse Events	129 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to imprecision	**RR 0.57** (0.33 to 0.86)	**587 per 1000**	**253 fewer per 1000** (from 82 fewer to 393 fewer)
Total Adverse Events	129 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to imprecision	**RR 0.83** (0.54 to 0.98)	**937 per 1000**	**159 fewer per 1000** (from 19 fewer to 431 fewer)
Transplant Rejection	129 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to imprecision	**RR 0.78** (0.43 to 1.27)	**349 per 1000**	**77 fewer per 1000** (from 199 fewer to 94 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 received Calcitriol, an active form of Vitamin D.

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

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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	⊕⊕⊕⊖ **MODERATE**	**RR 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 [23]; Lyles, et al., N Engl J Med. 2007; 357(18):1799-809 [24].

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome only assessed by one study

[2] Very small sample size

[3] 95% CI is very wide

PICO 5.6: 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 teriparatide, calcium, and vitamin D versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.7: 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 denosumab, calcium, and vitamin D versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.8: 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 active forms of vitamin D versus treatment with calcium and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.9: 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 oral bisphosphonate, calcium, and vitamin D?

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

SUMMARY of FINDINGS

Evidence Available:

Outcomes	No of Participants (studies) Follow up	Quality 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**[1,2,3] 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**[1,2,3] 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**[1,3] 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**[1,2,3] 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) 12 months	⨁⨁◯◯ **LOW**[1,3] due to imprecision	**RR 0.84** (0.24 to 2.91)	**116 per 1000**	**19 fewer per 1000** (from 88 fewer to 222 more)

Bibliography: Shane, et al. J Clin Endocrinol Metab. 2012 Dec; 97(12): 4481-90 [52]

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;

Evidence Available for Renal Transplant Recipients:

Outcomes	No of Participants (studies) Follow up	Quality 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	No data				
Non-Vertebral Fracture	No data				
Serious Adverse Events	No data				
Total Adverse Events	No data				

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**	**RR 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: Crandall, et al. AHRQ CER 53, March 2012; Tauchmanovà, 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]

GRADE Working Group grades of evidence

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

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

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

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

[1] Outcome only assessed by one study

[2] 95% CI is wide, crosses null effect

[3] Small sample size

PICO 5.10: 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 teriparatide, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.11: 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 denosumab, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.12: For post-menopausal women 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 raloxifene, calcium, and vitamin D versus treatment with oral bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.13: 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 teriparatide, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.14: 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 denosumab, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.15: For post-menopausal women 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 raloxifene, calcium, and vitamin D versus treatment with IV bisphosphonate, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.16: 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 oral bisphosphonates, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.17: 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 bisphosphonates, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.18: 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 teriparatide, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.19: 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 denosumab, calcium, and vitamin D versus treatment with activated vitamin D, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

PICO 5.20: 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 denosumab, calcium, and vitamin D versus treatment with teriparatide, calcium, and vitamin D?

This PICO was not directly addressed by any studies.

Recommendation: Because these individuals have near-normal kidney function (GFR threshold over ≥ 30 mL/min), the recommendations for organ transplant recipients are the same as those for adults not receiving transplants. Review available data for PICOs 1.1a-1.8a, 1.1b-1.18b, 1.1c-1.18c, 2.4-2.13, and 3.4-3.13 for best available evidence.

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Recommendation 10:
In Children ages 4-17 years treated with glucocorticoids for > 3 months, Treat with Calcium (1000 mg per day) and Vitamin D (600 IU per day) and Lifestyle Modifications over no Calcium and Vitamin D and over Oral Bisphosphonates

Based on PICOs: 7.1a and 7.2a

PICO 7.1a: 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?

Recommendation: Conditionally in favor of Supplementation with Calcium and Vitamin D over No Supplementation with Calcium and Vitamin D.

SUMMARY of FINDINGS

Bibliography:: Bak, et al. Pediatr Nephrol. 2006 Mar; 21(3):350-4 [53]; Choudhary, et al. Pediatr Nephrol. 2014 Jun;29(6):1025-32 [54]

Outcomes	No of Participants (studies) Follow up	Quality 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	41 (1 RCT) 12 weeks	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, indirectness, imprecision	**MD 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**[1,2,3,4] due to risk of bias, indirectness, imprecision	**MD -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^2	81 (2 RCTs) 10 weeks	⨁⊖⊖⊖ **VERY LOW**[1,2,3,5,6] due to risk of bias, inconsistency, indirectness, imprecision	**MD 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	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, indirectness, imprecision	**RR 0.75** (0.32 to 1.77)	**400 per 1000**	**100 fewer per 1000** (from 272 fewer to 308 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; **MD:** Mean difference

GRADE Working Group grades of evidence

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

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

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

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

[1] Participants/personnel not blinded to allocation. No placebo used

[2] Very small sample size

[3] Study duration is under 1 year. We agreed a priori to downgrade any study duration <12 mo for indirectness

[4] Outcome is only assessed by one study.

[5] I2=85%; due to significant differences in populations at baseline, direction of change is opposite between the two trials.

[6] 95% CI is wide

PICO 7.2a: 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?

Recommendation: Conditionally in favor of Calcium and Vitamin D over Oral Bisphosphonate + Calcium and Vitamin D.

SUMMARY of FINDINGS

Bibliography: 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]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D*	**Risk difference with Oral Bisphosphonate** (95% CI)**
Hip Fracture			No data		
Vertebral Fracture	128 (1 RCT) 12 months	⨁⨁⊖⊖ **LOW**[1,2,3,4] due to indirectness, imprecision	**RR 0.24** (0.03 to 2.11)	**63 per 1000**	**48 fewer per 1000** (from 62 fewer to 70 more)
Non-Vertebral Fracture	180 (3 RCTs) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,5] due to risk of bias, indirectness, imprecision	**RR 0.28** (0.05 to 1.63)	**45 per 1000**	**32 fewer per 1000** (from 43 fewer to 28 more)
Mean % Change in volumetric BMD (Lumbar Spine) g/cm^3	131 (2 RCTs) 12 months	⨁⨁⊖⊖ **LOW**[1,2,3] due to indirectness, imprecision	**MD 14.43** (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 **14.43 higher** (12.85 higher to 16.02 higher)
Change in BMD T score (Lumbar Spine)	30 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,4,5,6] due to risk of bias, indirectness, imprecision	**MD 0.80** (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 **0.80 higher**

					(0.46 higher to 1.14 higher)
Change in BMD Z score (Lumbar Spine)	18 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,4,6] due to indirectness, imprecision	**MD 0.24** (-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 **0.24 higher** (0.56 lower to 1.04 higher)
Serious Adverse Events			No data		
Total Adverse Events	128 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[2,4] due to indirectness, imprecision	**RR 0.87** (0.38 to 2.00)	**159 per 1000**	**21 fewer per 1000** (from 98 fewer to 159 more)
Hypocalcaemia	30 (1 RCT) 12 months	⊕⊖⊖⊖ **VERY LOW**[1,3,4,5,6] due to risk of bias, indirectness, imprecision	**RR 3.00** (0.13 to 68.26)	**0 per 1000**	**-**
Gastrointestinal Adverse Events	128 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[2,4] due to indirectness, imprecision	**RR 0.69** (0.23 to 2.07)	**111 per 1000**	**34 fewer per 1000** (from 86 fewer to 119 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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 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
[2] Participants in Bianchi 2013 are primarily taking inhalatory GCs (51%), only 30% of sample is taking both inhalatory and systemic GCs

[3] 95% CIs are wide

[4] Outcome is only assessed by one study

[5] El-Husseini is open label. Discontinuation is not reported.

[6] Very small sample size(s)

Recommendation 11:
In Children ages 4-17 with an osteoporotic fracture who are continuing treatment with glucocorticoids at a dose of ≥ 0.1 mg/kg for ≥ 3 months, Treat with Oral Bisphosphonates (IV bisphosphonate if oral treatment contraindicated) and Calcium and Vitamin D over Calcium and Vitamin D alone

Based on PICOs: 7.1b and 7.2b

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?

Recommendation: Conditionally in favor of Oral Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D.

SUMMARY of FINDINGS

Bibliography: 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]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium and Vitamin D*	Risk difference with Oral Bisphosphonate (95% CI)**
Hip Fracture			No data		
Vertebral Fracture	128 (1 RCT) 12 months	⨁⨁◯◯ **LOW**[1,2,3,4] due to indirectness, imprecision	**RR 0.24** (0.03 to 2.11)	**63 per 1000**	**48 fewer per 1000** (from 62 fewer to 70 more)
Non-Vertebral Fracture	180 (3 RCTs) 12 months	⨁◯◯◯ **VERY LOW**[1,2,3,5] due to risk of bias, indirectness, imprecision	**RR 0.28** (0.05 to 1.63)	**45 per 1000**	**32 fewer per 1000** (from 43 fewer to 28 more)
Mean % Change in volumetric BMD (Lumbar Spine) g/cm^3	131 (2 RCTs) 12 months	⨁⨁◯◯ **LOW**[1,2,3] due to indirectness, imprecision	**MD 14.43** (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 **14.43 higher** (12.85 higher to 16.02 higher)

Change in BMD T score (Lumbar Spine)	30 (1 RCT) 12 months	⊕⊖⊖⊖ **VERY LOW**[1,4,5,6] due to risk of bias, indirectness, imprecision	**MD 0.80** (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 **0.80 higher** (0.46 higher to 1.14 higher)
Change in BMD Z score (Lumbar Spine)	18 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[1,4,6] due to indirectness, imprecision	**MD 0.24** (-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 **0.24 higher** (0.56 lower to 1.04 higher)
Serious Adverse Events			No data		
Total Adverse Events	128 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[2,4] due to indirectness, imprecision	**RR 0.87** (0.38 to 2.00)	**159 per 1000**	**21 fewer per 1000** (from 98 fewer to 159 more)
Hypocalcaemia	30 (1 RCT) 12 months	⊕⊖⊖⊖ **VERY LOW**[1,3,4,5,6] due to risk of bias, indirectness, imprecision	**RR 3.00** (0.13 to 68.26)	**0 per 1000**	**-**
Gastrointestinal Adverse Events	128 (1 RCT) 12 months	⊕⊕⊖⊖ **LOW**[2,4] due to indirectness, imprecision	**RR 0.69** (0.23 to 2.07)	**111 per 1000**	**34 fewer per 1000** (from 86 fewer to 119 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;

GRADE Working Group grades of evidence

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

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

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

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

[1] 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

[2] Participants in Bianchi 2013 are primarily taking inhalatory GCs (51%), only 30% of sample is taking both inhalatory and systemic GCs

[3] 95% CIs are wide

[4] Outcome is only assessed by one study

[5] El-Husseini is open label. Discontinuation is not reported.

[6] Very small sample size(s)

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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of IV Bisphosphonate + Calcium and Vitamin D over Calcium and Vitamin D.

Recommendation 12:

In Adults ≥ age 40 continuing glucocorticoid treatment who have a fracture after 18 months of treatment with an oral bisphosphonate or significant loss of bone density (≥ 10% after 1 year of treatment), treat with another class of OP medication (teriparatide or denosumab) with Calcium and Vitamin D or use IV bisphosphonates if treatment failure is judged to be due to poor absorption or poor medication adherence over Calcium and Vitamin D alone

Based on PICOs: 10.1, 10.2, 10.3, 10.4, 10.5, and 10.6

PICO 10.1: For adults ≥ age 40 continuing chronic oral glucocorticoid treatment and who either have had a significant decline in bone density or sustained a new fracture after 18 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?

Recommendation: Conditionally in favor of Switching to an IV Bisphosphonate over Continuing an Oral Bisphosphonate

SUMMARY of FINDINGS

Evidence Available:

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Total Adverse Events			No data		

Bibliography: NA

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;

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality 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**[1] 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	⨁⨁⨁⊖ **MODERATE**[1] due to imprecision	**RR 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;

GRADE Working Group grades of evidence

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

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

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

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

[1] Outcome is only assessed by one study

PICO 10.2: For adults ≥ 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 18 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 oral bisphosphonate?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Switching to Teriparatide over Continuing an Oral Bisphosphonate

PICO 10.3: For adults ≥ 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 18 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 oral bisphosphonate?

Recommendation: Conditionally in favor of Switching to Denosumab over Continuing an Oral Bisphosphonate

SUMMARY of FINDINGS

Bibliography: Mok, et al. Bone. 2015 Jun;75:222-8 [59].

Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with Continuing Oral Bisphosphonate*	**Risk difference with Switching to Denosumab** (95% CI)**
Hip Fracture	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Hip Fracture in either group over 12 months	
Vertebral Fracture	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	
Non-Vertebral Fracture	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months	
Serious Adverse	42	⨁⊖⊖⊖	Not	No incidence of Serious Adverse Events	

Events	(1 RCT) 12 months	**VERY LOW**[1,2,3,4] due to risk of bias, imprecision	estimable	in either group over 12 months	
Total Adverse Events	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	**RR 3.6** (1.64 to 7.89)	**238 per 1000**	**619 more per 1000** (from 152 more to 1000 more)
Infections	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	**RR 7** (0.94 to 52.04)	**48 per 1000**	**286 more per 1000** (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;

[1] Open label trial

[2] Very small sample size

[3] Outcome only assessed by one study

[4] Due to zero events, effect was inestimable

Evidence Available for General Osteoporosis Population:

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	**Risk difference with Switching to Denosumab** (95% CI)**
Hip Fracture	821 (1 RCT) 12 months	⨁⨁⊖⊖ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 0.33** (0.01 to 8.14)	**2 per 1000**	**2 fewer per 1000** (from 2 fewer to 17 more)
Vertebral Fracture	1323 (2 RCTs) 12 months	⨁⨁⊖⊖ **LOW**[1,3,4] due to risk of bias, imprecision	**RR 1** (0.14 to 7.05)	**3 per 1000**	**0 fewer per 1000** (from 3 fewer to 18 more)
Non-Vertebral Fracture	1323 (2 RCTs) 12 months	⨁⨁⨁⊖ **MODERATE**[1] due to risk of bias	**RR 1.38** (0.71 to 2.67)	**23 per 1000**	**9 more per 1000** (from 7 fewer to 38 more)
Serious Adverse	2181	⨁⨁⨁⊖	**RR 1.17**	**67 per 1000**	**11 more per 1000**

Events	(3 RCTs) 12 months	**MODERATE**[1] due to risk of bias	(0.76 to 1.81)		(from 16 fewer to 54 more)
Total Adverse Events	2181 (3 RCTs) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias	**RR 0.98** (0.91 to 1.06)	**661 per 1000**	**13 fewer per 1000** (from 59 fewer to 40 more)
Infections	1323 (2 RCTs) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias	**RR 1.17** (0.95 to 1.45)	**150 per 1000**	**26 more per 1000** (from 8 fewer to 68 more)
Malignancies	2181 (3 RCTs) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias	**RR 0.86** (0.48 to 1.56)	**21 per 1000**	**3 fewer per 1000** (from 11 fewer to 12 more)

Bibliography: Kendler, et al. J Bone Miner Res. 20s10 Jan; 25(1):72-81 [60]. Recknor, et al. Obstet Gynecol. 2013 Jun; 121(6):1291-9. Roux, et al. Bone. 2014 Jan; 58: 48-54 [61].

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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Open label trial(s)
[2] Outcome is only assessed by one study
[3] 95% CI is wide
[4] Due to zero events, the effect of one trial is inestimable

PICO 10.4: For adults ≥ 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 18 months of an oral bisphosphonate, what are the benefits and harms of switching to IV bisphosphonate (though continuing calcium and vitamin D) compared switching to teriparatide?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Switching to Teriparatide over Switching to an IV Bisphosphonate

PICO 10.5: For adults ≥ 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 18 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Switching to an IV Bisphosphonate over Switching to Denosumab

PICO 10.6: For adults ≥ 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 18 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Switching to Denosumab over Switching to Teriparatide

Recommendation 13:
In Adults ≥ 40 years who have completed bisphosphonate treatment (3-5 years) yet remain at High or Moderate Risk of Fracture who continue GC treatment, continue bisphosphonate treatment over discontinuing bisphosphonates.

Based on PICOs: 12.1, 12.2, 12.3, 12.4, 12.5, and 12.6

PICO 12.1: For adults at High Risk of Fracture continuing chronic oral glucocorticoid treatment who have completed 5 years of oral bisphosphonate 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)?

Recommendation: Conditionally in favor of Continuing an Oral Bisphosphonate + Calcium and Vitamin D over Stopping osteoporosis medication, but continuing Calcium and Vitamin D

SUMMARY of FINDINGS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	**Risk difference with Discontinuing Oral Bisphosphonate** (95% CI)**
Hip Fracture				No data	
Vertebral Fracture				No data	
Non-Vertebral Fracture				No data	
Serious Adverse Events				No data	
Total Adverse Events				No data	
Bibliography: NA					

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;

Evidence Available for 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	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate*	**Risk difference with Discontinuing Oral Bisphosphonate** (95% CI)**
Hip Fracture	1099 (1 RCT) 5 years	⨁⨁⨁⨀ **MODERATE**[1] due to imprecision	**RR 0.98** (0.5 to 1.96)	**30 per 1000**	**1 fewer per 1000** (from 15 fewer to 29 more)
Vertebral Fracture	1449 (2 RCTs) 3.5 years	⨁⨁⨁⨁ **HIGH**	**RR 1.15** (0.82 to 1.6)	**84 per 1000**	**13 more per 1000** (from 15 fewer to 50 more)
Non-Vertebral Fracture	1515 (3 RCTs) 3 years	⨁⨁⨁⨀ **MODERATE**[2] due to risk of bias	**RR 1.03** (0.81 to 1.3)	**153 per 1000**	**5 more per 1000** (from 29 fewer to 46 more)
Serious Adverse Events	350 (1 RCT) 2 years	⨁⨁⨁⨀ **MODERATE**[1] due to imprecision	**RR 1.39** (0.75 to 2.58)	**94 per 1000**	**37 more per 1000** (from 23 fewer to 148 more)
Total Adverse Events	350 (1 RCT) 2 years	⨁⨁⨁⨀ **MODERATE**[1] due to imprecision	**RR 1.03** (0.95 to 1.11)	**881 per 1000**	**26 more per 1000** (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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome only assessed by one study
[2] One trial includes an open label arm

PICO 12.2: For adults at High Risk of Fracture continuing chronic oral glucocorticoid treatment who have completed 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)?

Recommendation: Conditionally in favor of Switching to an IV Bisphosphonate + Calcium and Vitamin D over Continuing an Oral Bisphosphonate + Calcium and Vitamin D

SUMMARY of FINDINGS

Outcomes	No of Participants (studies) Follow up	Quality 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			No data		
Total Adverse Events			No data		
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Bibliography: McClung, et al. Bone. 2007 Jul; 41(1):122-8. [58]

Outcomes	No of Participants (studies) Follow up	Quality 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**[1] 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	⨁⨁⨁⊖ **MODERATE**[1] 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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is only assessed by one study

PICO 12.3: For adults at High Risk of Fracture continuing chronic oral glucocorticoid treatment who have 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)?

Recommendation: Conditionally in favor of Switching to an osteoporosis medication of another class + Calcium and Vitamin D over Continuing an Oral Bisphosphonate + Calcium and Vitamin D

***All participants included in studies which comprise GIOP and General Osteoporosis evidence provided below switched from Oral Bisphosphonate to Denosumab**

SUMMARY of FINDINGS

Bibliography: Mok, et al. Bone. 2015 Jun;75:222-8. [59]

Outcomes	No of Participants (studies) Follow up	Quality 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	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Hip Fracture in either group over 12 months	
Vertebral Fracture	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	
Non-Vertebral Fracture	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months	
Serious Adverse Events	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Serious Adverse Events in either group over 12 months	

Total Adverse Events	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	**RR 3.6** (1.64 to 7.89)	**238 per 1000**	**619 more per 1000** (from 152 more to 1000 more)
Infections	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	**RR 7** (0.94 to 52.04)	**48 per 1000**	**286 more per 1000** (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;

[1] Open label trial

[2] Very small sample size

[3] Outcome only assessed by one study

[4] Due to zero events, effect was inestimable

Evidence Available for 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 [65]

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⊖⊖ **LOW**[1,2,3] 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	⨁⨁⊖⊖ **LOW**[1,2,4] due to risk of bias, imprecision	**RR 1.97** (0.6 to 6.45)	**16 per 1000**	**16 more per 1000** (from 6 fewer to 88 more)
Serious Adverse	1360	⨁⨁⨁⊖	**RR 0.94**	**75 per 1000**	**5 fewer per**

Events	(2 RCTs) 12 months	**MODERATE**[1] due to risk of bias	(0.64 to 1.37)		**1000** (from 27 fewer to 28 more)
Total Adverse Events	1360 (2 RCTs) 12 months	⨁⨁⨁⊖ **MODERATE**[1] due to risk of bias	**RR 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	⨁⨁⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 1.17** (0.95 to 1.45)	**373 per 1000**	**63 more per 1000** (from 19 fewer to 168 more)
Malignancies	1360 (2 RCTs) 12 months	⨁⨁⨁⊖ **MODERATE**[1] due to risk of bias	**RR 0.88** (0.44 to 1.74)	**25 per 1000**	**3 fewer per 1000** (from 14 fewer to 19 more)
Death	1360 (2 RCTs) 12 months	⨁⨁⊖⊖ **LOW**[1,4] due to risk of bias, imprecision	**RR 0.99** (0.1 to 9.52)	**1 per 1000**	**0 fewer per 1000** (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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Open label trial(s)
[2] Outcome only assessed by one study
[3] Due to zero events, effect of one or more study(ies) is inestimable
[4] 95%CI is wide

PICO 12.4: For adults at Moderate Risk of Fracture continuing chronic oral glucocorticoid treatment who have completed 5 years of oral bisphosphonate 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)?

Recommendation: Conditionally in favor of Continuing an Oral Bisphosphonate + Calcium and Vitamin D over Stopping osteoporosis medication, but continuing Calcium and Vitamin D

SUMMARY of FINDINGS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate	**Risk difference with Discontinuing Oral Bisphosphonate** (95% CI)
Hip Fracture				No data	
Vertebral Fracture				No data	
Non-Vertebral Fracture				No data	
Serious Adverse Events				No data	
Total Adverse Events				No data	
Bibliography: NA					

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;

Evidence Available for 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	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing Oral Bisphosphonate	**Risk difference with Discontinuing Oral Bisphosphonate** (95% CI)
Hip Fracture	1099 (1 RCT)	⨁⨁⨁⊖ **MODERATE**[1]	**RR 0.98** (0.5 to 1.96)	**30 per 1000**	**1 fewer per 1000**

	5 years	due to imprecision			(from 15 fewer to 29 more)
Vertebral Fracture	1449 (2 RCTs) 3.5 years	⊕⊕⊕⊕ **HIGH**	**RR 1.15** (0.82 to 1.6)	**84 per 1000**	**13 more per 1000** (from 15 fewer to 50 more)
Non-Vertebral Fracture	1515 (3 RCTs) 3 years	⊕⊕⊕⊖ **MODERATE**[2] due to risk of bias	**RR 1.03** (0.81 to 1.3)	**153 per 1000**	**5 more per 1000** (from 29 fewer to 46 more)
Serious Adverse Events	350 (1 RCT) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 1.39** (0.75 to 2.58)	**94 per 1000**	**37 more per 1000** (from 23 fewer to 148 more)
Total Adverse Events	350 (1 RCT) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 1.03** (0.95 to 1.11)	**881 per 1000**	**26 more per 1000** (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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome only assessed by one study
[2] One trial includes an open label arm

PICO 12.5: For adults at Moderate Risk of Fracture continuing chronic oral glucocorticoid treatment who have completed 5 years of oral bisphosphonate and, 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)?

Recommendation: Conditionally in favor of Switching to an IV Bisphosphonate+Calcium and Vitamin D over Continuing an Oral Bisphosphonate+Calcium and Vitamin D

SUMMARY of FINDINGS

Outcomes	No of Participants (studies) Follow up	Quality 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				No data	
Total Adverse Events				No data	
Bibliography: NA					

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;

Evidence Available for General Osteoporosis Population:

Bibliography: McClung, et al. Bone. 2007 Jul; 41(1):122-8. [58]

Outcomes	No of Participants (studies) Follow up	Quality 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**[1] 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	⨁⨁⨁⊖ **MODERATE**[1] 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;

GRADE Working Group grades of evidence

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

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

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

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

[1] Outcome is only assessed by one study

PICO 12.6: For adults at Moderate Risk of Fracture continuing chronic oral glucocorticoid treatment who have completed 5 years of oral bisphosphonate 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 switching to an osteoporosis medication in a different drug class (though continuing calcium and vitamin D)?

Recommendation: Conditionally in favor of Switching to an osteoporosis medication of another class + Calcium and Vitamin D over Continuing an Oral Bisphosphonate + Calcium and Vitamin D

***All participants included in studies which comprise GIOP and General Osteoporosis evidence provided below switched from Oral Bisphosphonate to Denosumab**

SUMMARY of FINDINGS

Bibliography: Mok, et al. Bone. 2015 Jun;75:222-8. [59]

Outcomes	No of Participants (studies) Follow up	Quality 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	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Hip Fracture in either group over 12 months	
Vertebral Fracture	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Vertebral Fracture in either group over 12 months	
Non-Vertebral Fracture	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Non-Vertebral Fracture in either group over 12 months	
Serious Adverse Events	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	Not estimable	No incidence of Serious Adverse Events in either group over 12 months	
Total	42	⨁⊖⊖⊖	**RR 3.6**	**238 per 1000**	**619 more per 1000**

Adverse Events	(1 RCT) 12 months	**VERY LOW**[1,2,3] due to risk of bias, imprecision	(1.64 to 7.89)		(from 152 more to 1000 more)
Infections	42 (1 RCT) 12 months	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	**RR 7** (0.94 to 52.04)	**48 per 1000**	**286 more per 1000** (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;

[1] Open label trial

[2] Very small sample size

[3] Outcome only assessed by one study

[4] Due to zero events, effect was inestimable

Evidence Available for 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 [65]

Outcomes	No of Participants (studies) Follow up	Quality 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	⨁⨁⊖⊖ **LOW**[1,2,3] 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	⨁⨁⊖⊖ **LOW**[1,2,4] due to risk of bias, imprecision	**RR 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	⨁⨁⨁⊖ **MODERATE**[1] due to risk of bias	**RR 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	⨁⨁⨁⨀ **MODERATE**[1] due to risk of bias	**RR 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	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	**RR 1.17** (0.95 to 1.45)	**373 per 1000**	**63 more per 1000** (from 19 fewer to 168 more)
Malignancies	1360 (2 RCTs) 12 months	⨁⨁⨁⨀ **MODERATE**[1] due to risk of bias	**RR 0.88** (0.44 to 1.74)	**25 per 1000**	**3 fewer per 1000** (from 14 fewer to 19 more)
Death	1360 (2 RCTs) 12 months	⨁⨁⨀⨀ **LOW**[1,4] due to risk of bias, imprecision	**RR 0.99** (0.1 to 9.52)	**1 per 1000**	**0 fewer per 1000** (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;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Open label trial(s)
[2] Outcome only assessed by one study
[3] Due to zero events, effect of one or more study(ies) is inestimable
[4] 95%CI is wide

Recommendations 14 and 15:
In Adults ≥ 40 years taking an osteoporosis medication in addition to calcium and Vitamin D who discontinue glucocorticoid treatment and are assessed to be of low risk of fracture, Discontinue the OP medication but continue Calcium and Vitamin D over continuing the OP medication.

In Adults ≥ 40 years taking an osteoporosis medication in addition to calcium and Vitamin D who discontinue glucocorticoid treatment and are assessed to be of moderate to high risk of fracture, complete the course of the OP medication with Calcium and Vitamin D over discontinuing the OP medication

The following PICOs were reviewed and subject to voting by a Panel of Experts in order to determine this recommendation: 11.1, 11.2, and 11.3

PICO 11.1: For adults ≥ age 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Stopping the current osteoporosis medication over Continuing the current medication. The recommendation was made by expert consensus. The evidence informing this was indirect and was of very low quality.

PICO 11.2: For adults ≥ age 40 taking osteoporosis medication in addition to calcium and vitamin D, and discontinuing oral glucocorticoid therapy and assessed to be of moderate 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?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Continuing the current osteoporosis medication over Stopping the current medication. The recommendation was made by expert consensus. The evidence informing this was indirect and was of very low quality

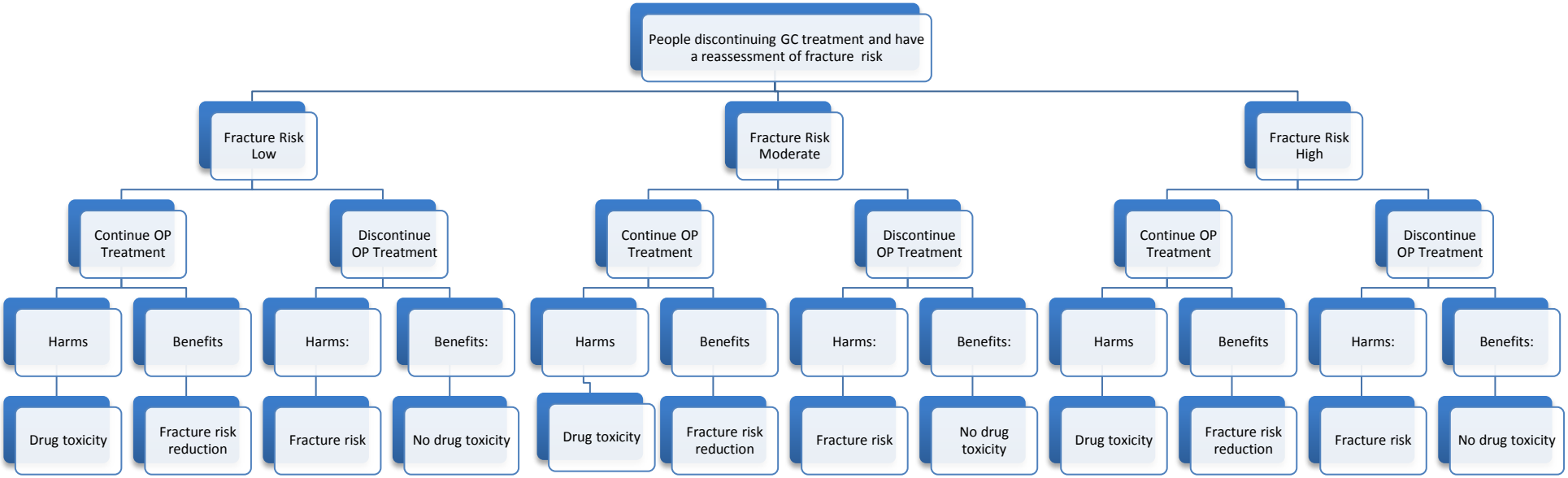
PICO 11.3: For adults ≥ age40 taking osteoporosis medication in addition to calcium and vitamin D, and discontinuing oral glucocorticoid therapy and assessed to be of high fracture risk, what are the

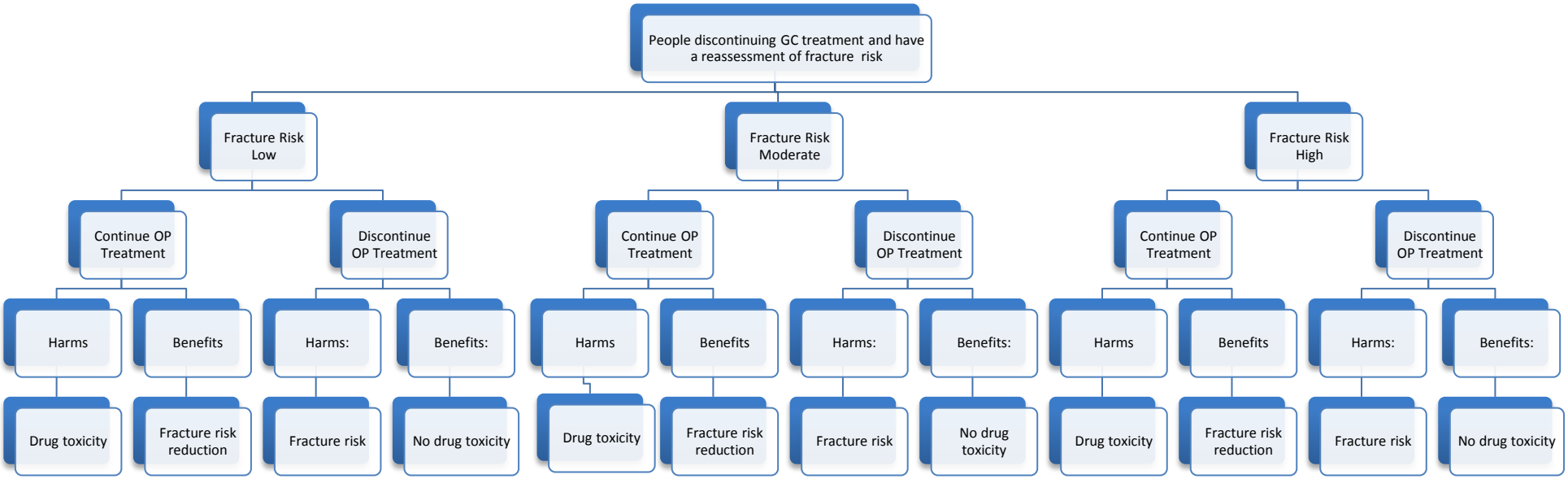
benefits and harms of stopping the current osteoporosis medication (though continuing calcium and vitamin D) compared to continuing current osteoporosis medication?

This PICO was not directly addressed by any studies.

Recommendation: Conditionally in favor of Continuing the current osteoporosis medication over Stopping the current medication. The recommendation was made by expert consensus. The evidence informing this was indirect and was of very low quality

Algorithm for PICOs 11.1-11.3:




People discontinuing GC treatment and have a reassessment of fracture risk
Fracture Risk Low
Fracture Risk Moderate
Fracture Risk High
Continue OP Treatment
Discontinue OP Treatment
Continue OP Treatment
Discontinue OP Treatment
Continue OP Treatment
Discontinue OP Treatment
Harms
Benefits
Harms:
Benefits:
Harms
Benefits
Harms:
Benefits:
Harms
Benefits
Harms:
Benefits:
Drug toxicity
Fracture risk reduction
Fracture risk
No drug toxicity
Drug toxicity
Fracture risk reduction
Fracture risk
No drug toxicity
Drug toxicity
Fracture risk reduction
Fracture risk
No drug toxicity

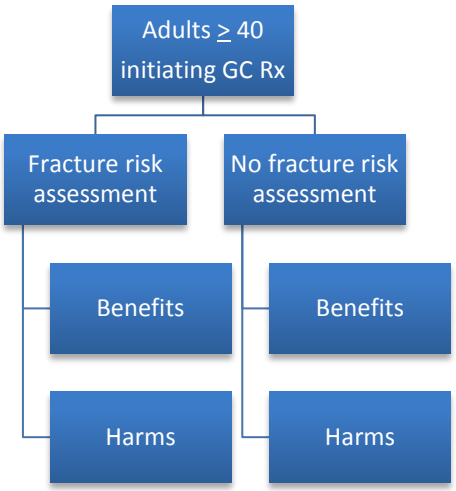
INITIAL FRACTURE RISK ASSESSMENT VERSUS NO FRACTURE RISK ASSESSMENT

ADULTS ≥ 40

PICO 8.1: In adults ≥ age 40 who are initiating or continuing oral glucocorticoid therapy expected to last ≥ 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

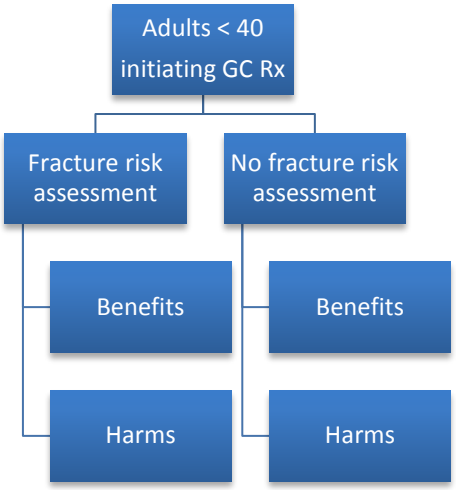
Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.

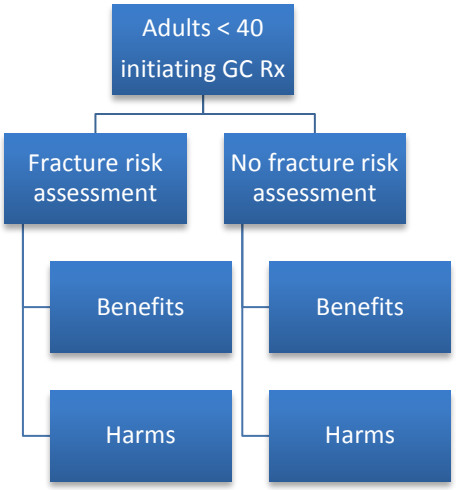


ICO 8.2: In adults < age 40 who are initiating or continuing oral glucocorticoid therapy expected to last ≥ 90 days, but who never have had an assessment of fracture risk or been treated with osteoporosis medication, what are the benefits and harms of patient fracture risk assessment (e.g., FRAX, BMD, VFA, spine x-rays, symptomatic fracture history) (including timing) versus no fracture risk assessment?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.


Adults < 40 initiating GC Rx
Fracture risk assessment
No fracture risk assessment
Benefits
Harms
Benefits
Harms



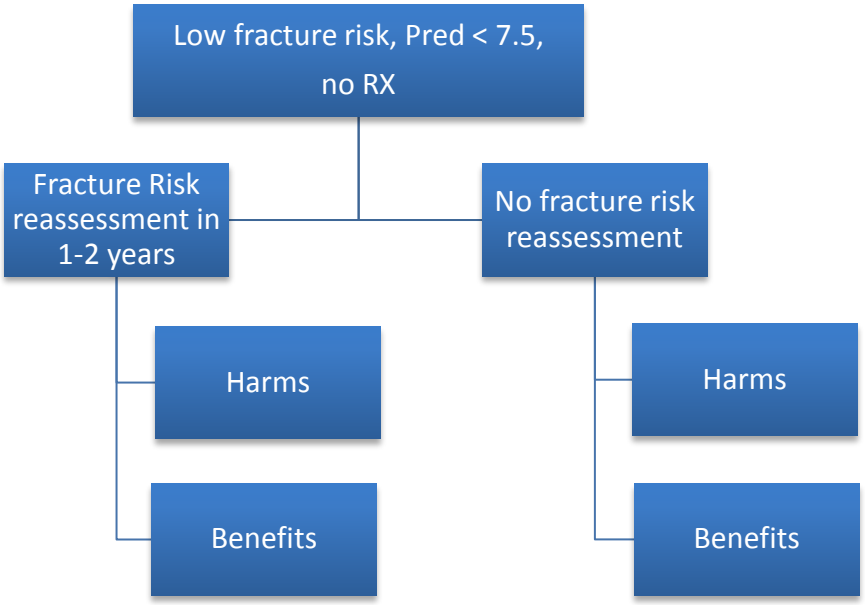
FRACTURE RISK REASSESSMENT QUESTIONS (YES-NO)

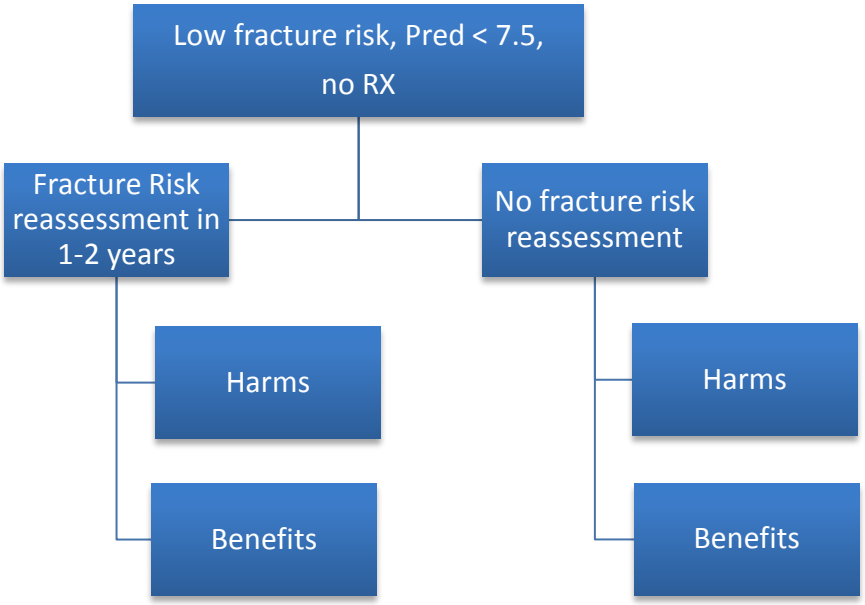
Untreated/Low risk – either not recommended or recommended but not treated/ low or high dose

PICO 9.1: In adults ≥ age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose <7.5 mg daily, assessed low fracture risk) who were not recommended to start or otherwise didn't 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.



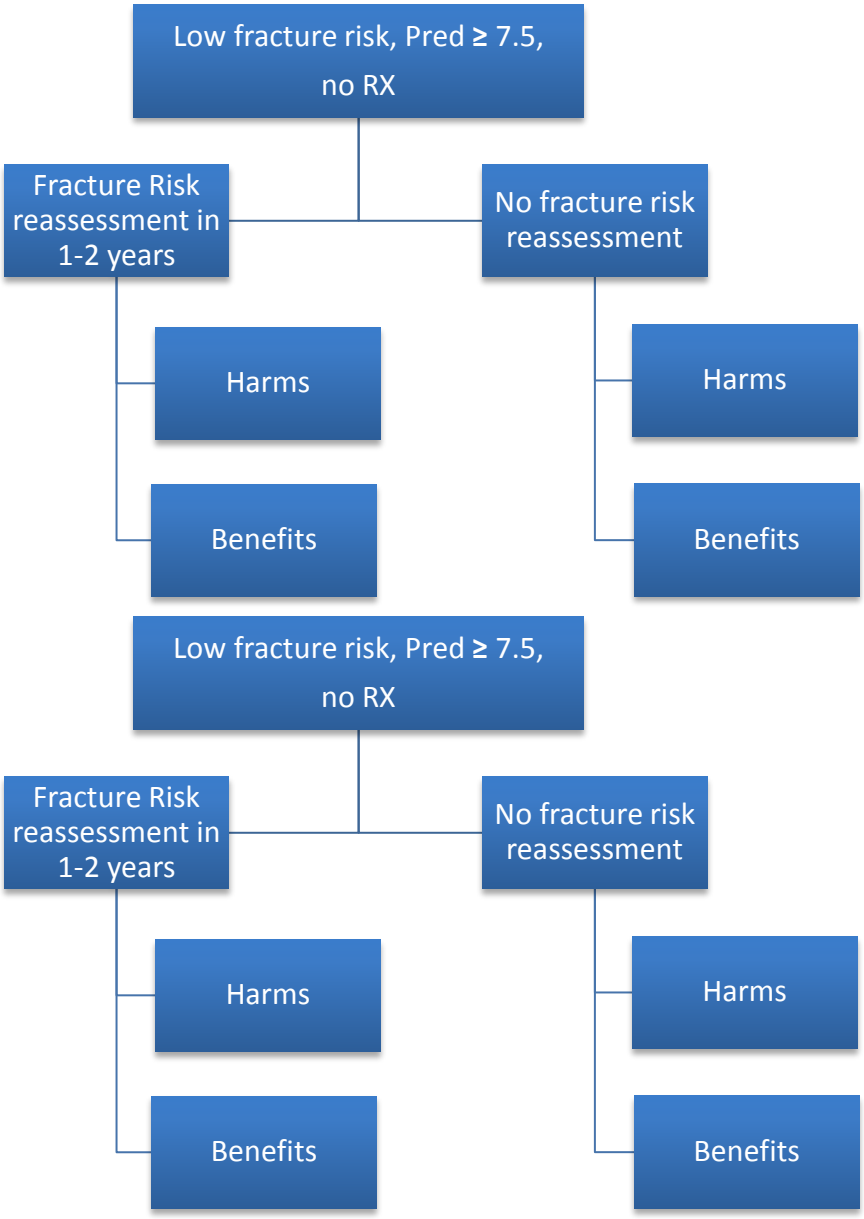


PICO 9.2: In adults ≥ age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose ≥ 7.5 mg daily, assessed low fracture risk) who were not recommended to start or

otherwise didn't 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.

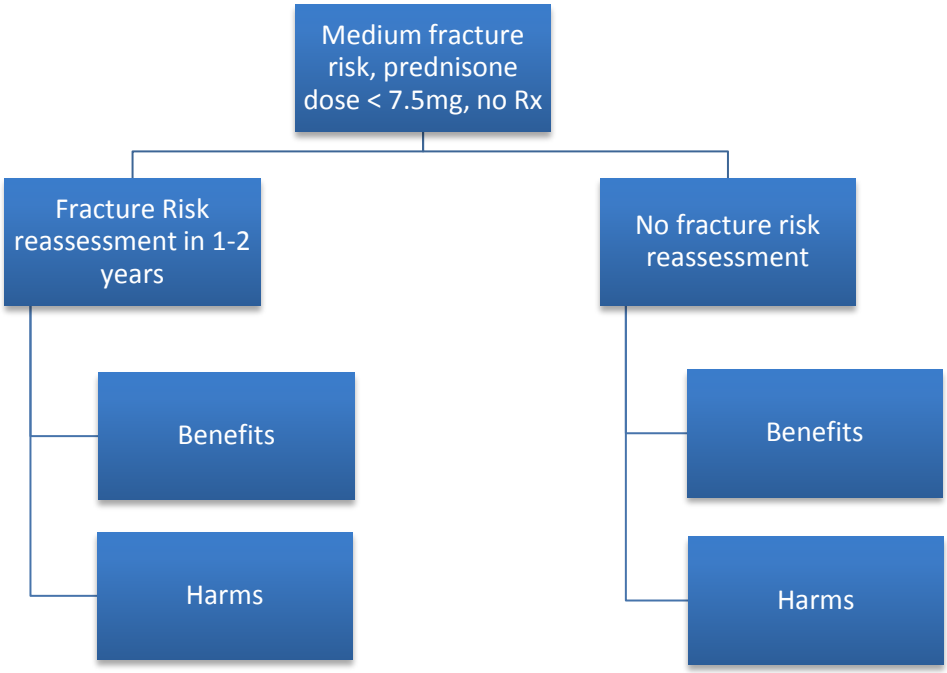


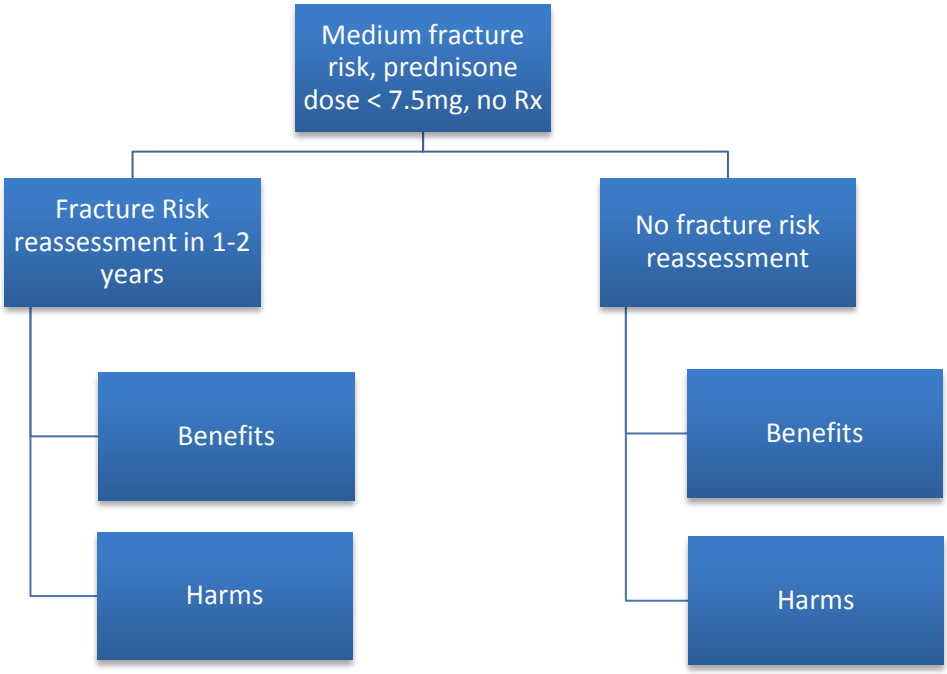
Untreated/Mod risk – either not recommended or recommended but not treated/low dose or high dose

PICO 9.3: In adults ≥ age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose <7.5 mg daily, assessed medium fracture risk) who were not recommended to start or otherwise didn't 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.

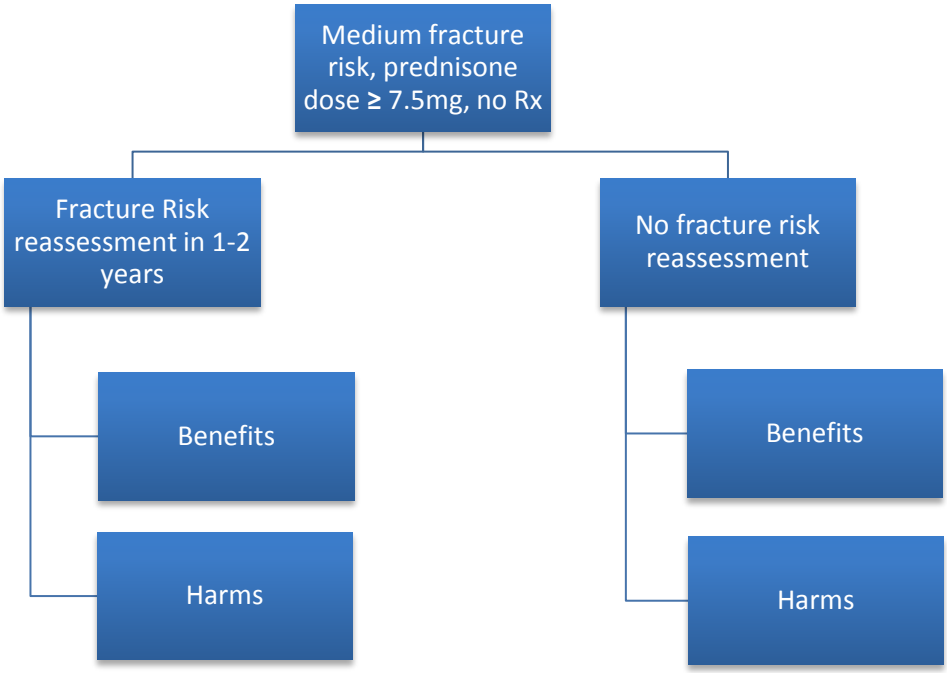




PICO 9.4: In adults ≥ age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose ≥ 7.5 mg daily, assessed medium fracture risk) who were not recommended to start or otherwise didn't start osteoporosis medication (except calcium and vitamin D), what are the benefits and harms 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.



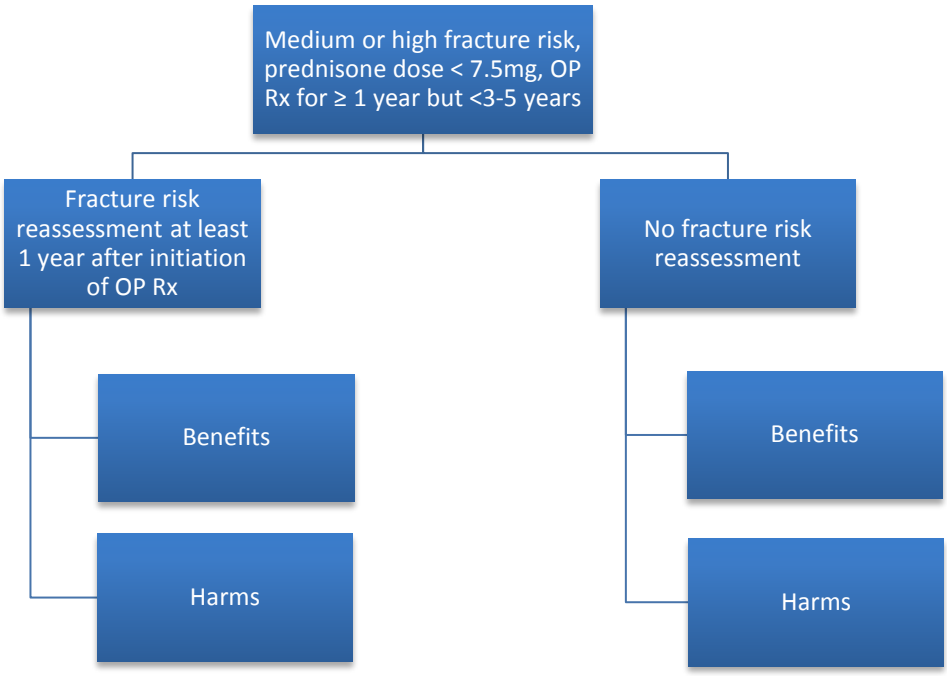
Medium fracture risk, prednisone dose ≥ 7.5mg, no Rx
Fracture Risk reassessment in 1-2 years
No fracture risk reassessment
Benefits
Harms
Benefits
Harms

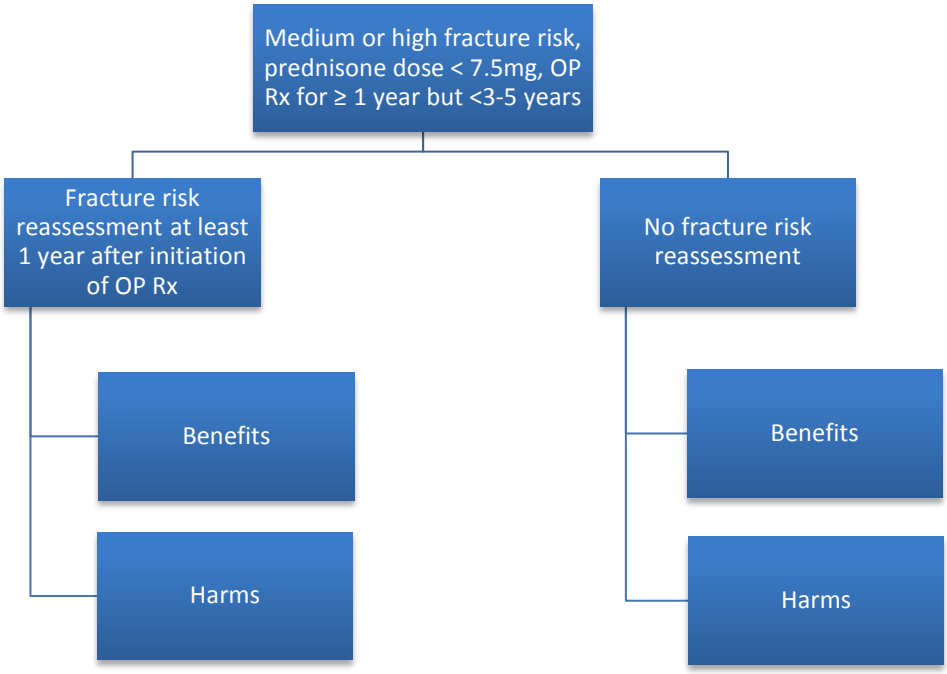
Adults currently taking GIOP Treatment, looking at reassessment to decide whether to continue current treatment, stop treatment or change treatment: *Reassessment/no reassessment, high and low dose*

PICO 9.5: In adults ≥ 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 ≥ 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.

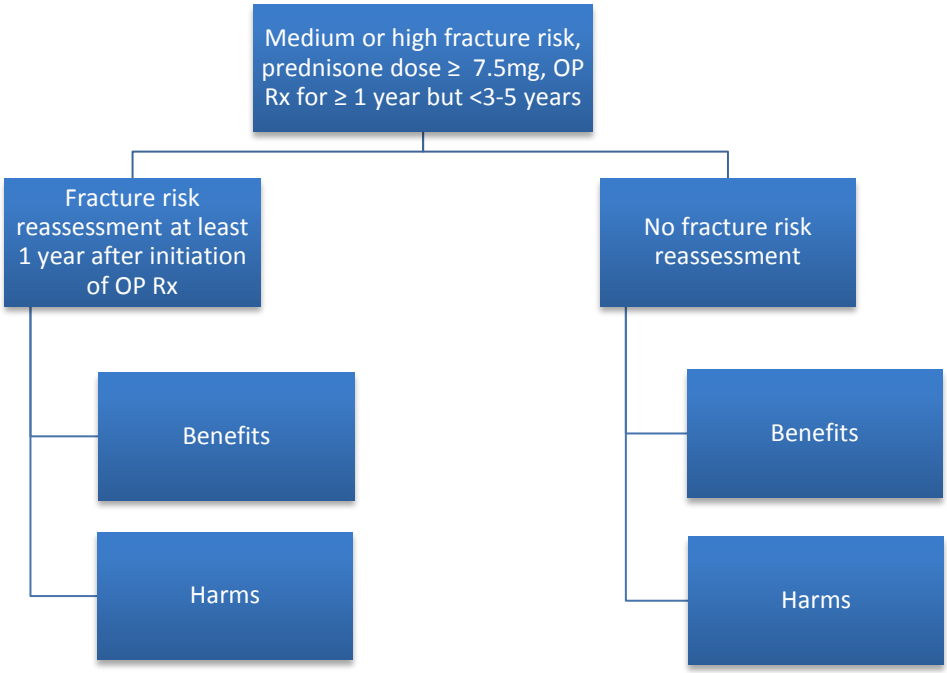




PICO 9.6: In adults ≥ age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose ≥ 7.5 mg daily, medium or high fracture risk assessment), continuing osteoporosis medication for ≥ 1 year but 5 years, what are the benefits and harms of any reassessment of patient fracture risk (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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.



Medium or high fracture risk, prednisone dose ≥ 7.5mg, OP Rx for ≥ 1 year but <3-5 years
Fracture risk reassessment at least 1 year after initiation of OP Rx
No fracture risk reassessment
Benefits
Harms
Benefits
Harms

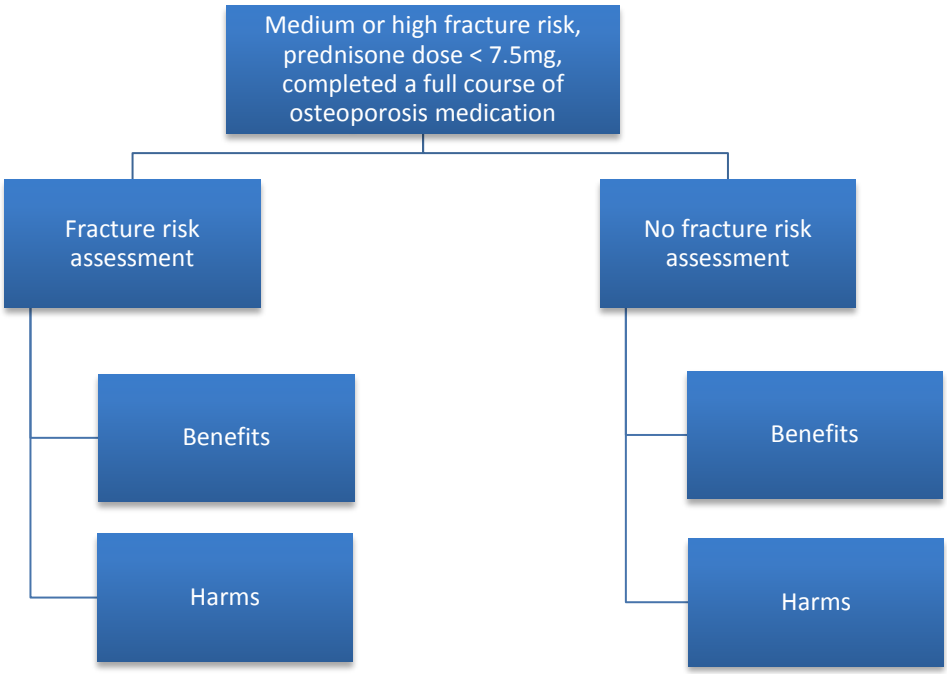
FRACTURE RISK REASSESSMENT QUESTIONS AFTER COMPLETING A FULL COURSE OF OP MEDICATION - (YES/NO, EARLY/LATE, HIGH AND LOW DOSE)

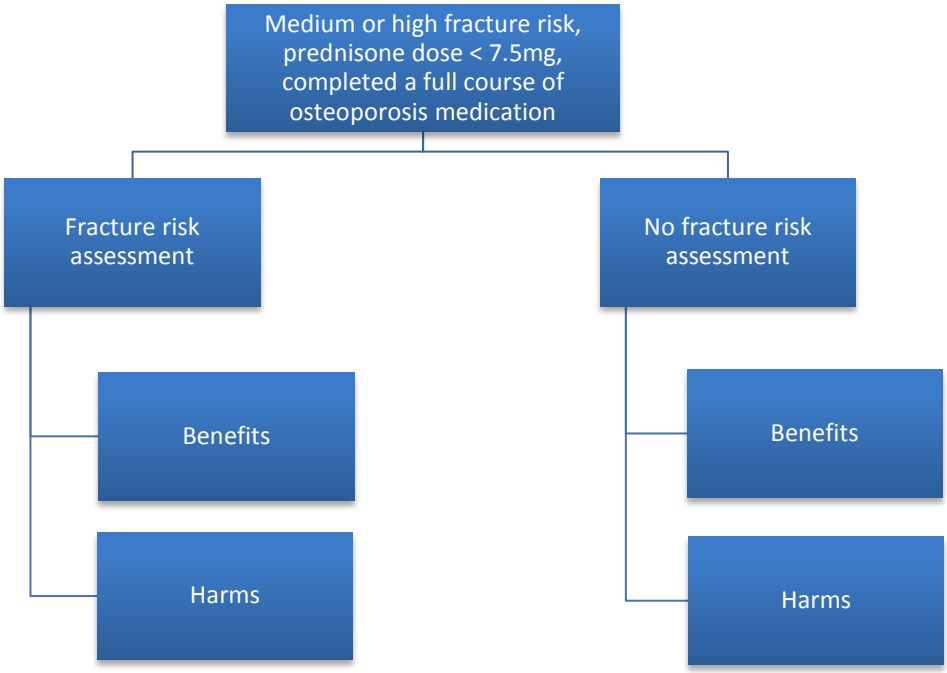
YES/NO

PICO 9.7: In adults ≥ 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 (e.g., 3-5 years of oral bisphosphonate), 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.

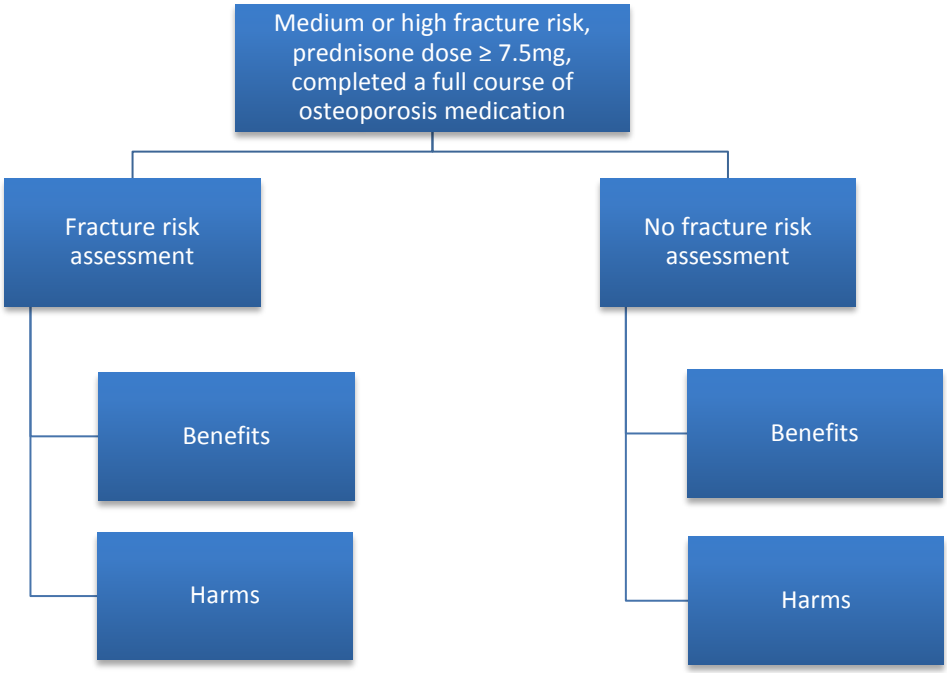




PICO 9.8: In adults ≥ age 40 continuing chronic oral glucocorticoid treatment (mean current prednisone dose ≥ 7.5 mg daily, assessed as medium or high fracture risk), and who have completed a full course of osteoporosis medication (e.g., 3-5 years of oral bisphosphonate), what are the benefits and harms 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?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.



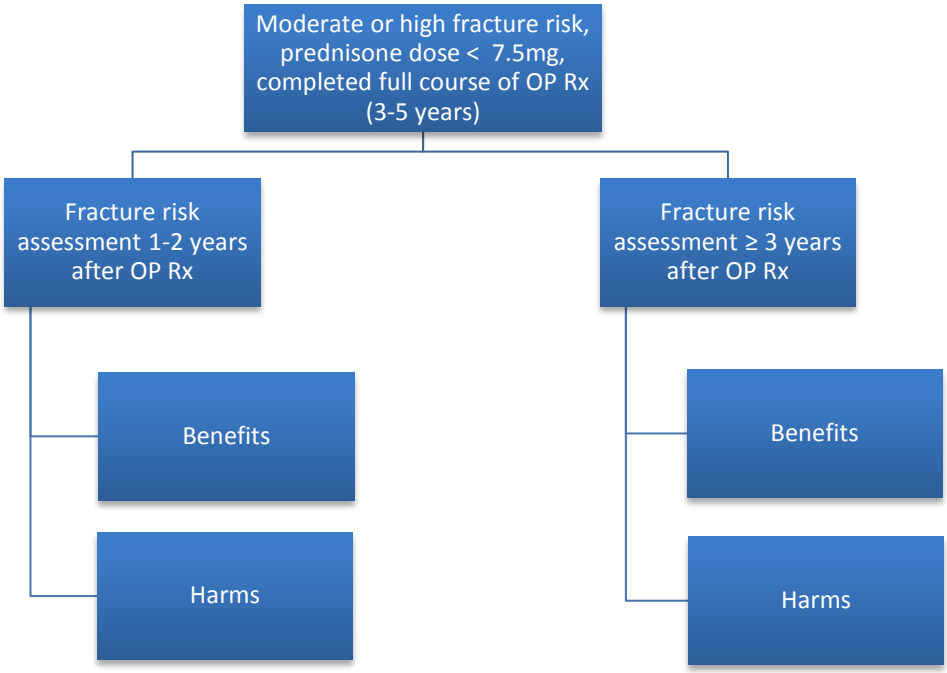
Medium or high fracture risk, prednisone dose ≥ 7.5mg, completed a full course of osteoporosis medication
Fracture risk assessment
No fracture risk assessment
Benefits
Harms
Benefits
Harms

Timing: EARLY/LATE

PICO 9.9: In adults ≥ 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 (e.g., 3-5 years of oral bisphosphonate), 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., ≥ 3 years after the osteoporosis medication was stopped)?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.

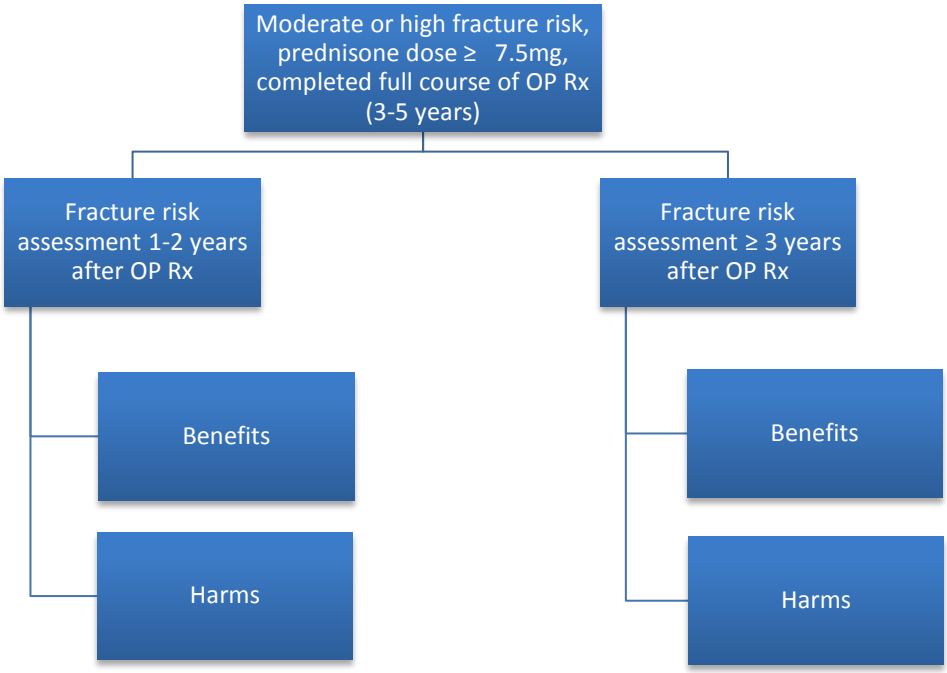


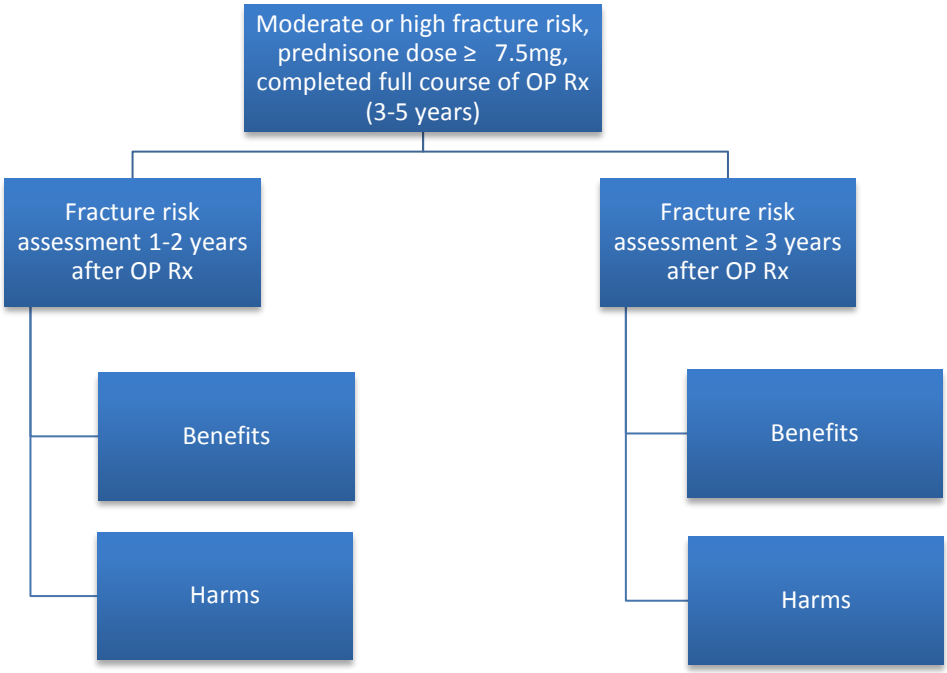
Moderate or high fracture risk, prednisone dose < 7.5mg, completed full course of OP Rx (3-5 years)
Fracture risk assessment 1-2 years after OP Rx
Fracture risk assessment ≥ 3 years after OP Rx
Benefits
Harms
Benefits
Harms

PICO 9.10: In adults ≥ 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 (e.g., 3-5 years of oral bisphosphonate), 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., ≥ 3 years after the osteoporosis medication was stopped)?

This PICO was not directly addressed by any studies. Therefore, an algorithm of viable treatment options and their associated harms and benefits was constructed and is shown below.

Quality of evidence across all critical outcomes: Very low ⨁⊖⊖⊖. No data were available to address this question.


Moderate or high fracture risk, prednisone dose ≥ 7.5mg, completed full course of OP Rx (3-5 years)
Fracture risk assessment 1-2 years after OP Rx
Fracture risk assessment ≥ 3 years after OP Rx
Benefits
Harms
Benefits
Harms


Moderate or high fracture risk, prednisone dose ≥ 7.5mg, completed full course of OP Rx (3-5 years)
Fracture risk assessment 1-2 years after OP Rx
Fracture risk assessment ≥ 3 years after OP Rx
Benefits
Harms
Benefits
Harms

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